THE PROCEEDINGS

of the

Institute of Medicine of Chicago

Vol. 3 No. 1

CHICAGO
1920

THE PATIENT HIMSELF

Hugh T. Patrick

President's Address
Dec. 1, 1919

Among the vices of advancing years are carping criticism, garrulity and needless admonition. To all of these I plead guilty and so can only beg your indulgence while I say a few things that I think should be said, knowing that I say them poorly and that I add nothing to our store of knowledge.

My theme is that much neglected individual, the patient himself. Concerning his organs and their functions, we have numberless tomes. Concerning the diseases that attack his parts, we have whole libraries. Concerning the various ways of cutting him open and sewing him up, there are several six-foot shelves. For the manifold instruments, machines and appliances of our armamentarium, an extensive congeries of industries is in constant operation. Indeed, some of us are so used to practicing medicine by machinery that the cortical cell bids fair to shrink into sterile desuetude. But of the patient himself — the man, the woman, the child — relatively little is thought or written.

THE PATIENT ABOVE THE EYEBROWS

What do I mean by the patient himself? I mean what we mean when we speak of our friend, our enemy, our son, our daughter. We like a man because he is sensible, kind or entertaining; dislike him because he is selfish, irritable or pessimistic. So do we admire or despise because of certain mental, not physical, qualities: traits that reside above the eyebrows. Our atttitude depends on the individual's personality: the biggest thing to us and to him. It is more important than his kidneys and his liver, and its disorders are as momentous to him and to society as is disease of his organs. His personality is what he is — the man himself; and he is the sum of all his tendencies and experiences; his desires, aversions, affections, hates, passions, inhibitions, appetites, reflections and knowledge. The tendencies are few and simple, the experiences myriad. A little thought shows that most of this experience has been in the form of conflicts. From the beginning, life is a conflict: an effort to live and be happy — that is to say,

an effort to adapt ourselves to the conditions under which we must live. The struggle between what we consciously or unconsciously wish to do, and what the present state of society requires us to do begins in infancy and never stops. Very early the normal child learns that certain perfectly natural functions may not be fulfilled in a completely natural way. He may not urinate in the parlor, nor appropriate anything he happens to see. As we grow older, these conflicts become more complex and more acute. Some of us come out of them pretty much to the satisfaction of ourselves and our neighbors. We are the happy, the well and the successful. Some of us are unable to make the adjustment. We, then, are the unhappy, the ill or the unsuccessful. Now, as every one of us has these conflicts and has them all the time, it does not take much perspicacity to see that there are many defeats. Occasionally one comes out of the conflict a thief, a tramp, a pauper, an invalid. Probably one does not think of petty larceny, constipation and eye strain in the same terms; but they may be equally due to social inadaptability. Each is the reaction to a difficult situation.

THE RESULTS OF MALADAPTATION

The whole question of health is one of adaptation or adaptability. We have typhoid fever either because individually we are still vulnerable to the typhoid germ, or because as a community we have failed successfully to combat it. Some of us have neuroses or psychoses because we are unable successfully to harmonize with our environment — *and for no other reason.* Often this fact is overlooked. What has social inadequacy to do with the practice of medicine? *A great deal,* because it starts a multiplicity of symptoms which the patient expects the physician to relieve. To speak of the hyperacidity and gastric distress of financial insufficiency, the dysmenorrhea of domestic disharmony and the tachycardia of industrial futility may sound incongruous, but sometimes that is what they are.

An easy approach to consideration of the neuroses as a result of maladaptation, that is to say, as the outcome of a conflict, is by way of the war neuroses because there the conflict is so apparent. A war neurosis, grossly miscalled shell shock, is a means of, let us say, getting out of the front line trenches. The soldier can no longer stand the bursting shells, the falling parapets, the horrible sights and the imminent danger of death. But army discipline and morale, personal honor, pride, ideals make running away impossible. A neurosis makes

it possible. So does loss of an arm. If he loses an arm, the soldier doesn't have a neurosis. A neurosis is no fun, but it is a great deal better than the trenches.

Peace neuroses are just the same. They are a way out of trouble or around an obstacle; a way selected more or less unconsciously. If one cannot remove an obstacle from his path and cannot surmount it, he goes around. Perhaps he *can* push it away, or *can* surmount it; but he *prefers* to go around. For our patients, the way around is often insomnia, "nervous breakdown," backache, dysmenorrhea, asthenopia, indigestion, headache, abdominal pain, dyspareunia, impotence, exhaustion, palpitation and many other things for which medicines are given and operations performed.

As already indicated, a neurosis is by no means the only avenue of escape from an intolerable or uncomfortable situation. Some ways are much simpler. The man who, when tired of his job and dissatisfied with his wife, stops work, gets drunk and beats up his connubial partner, does not develop a neurosis from those particular troubles. He doesn't have to. But he is just the one to get a lame back or sore feet in the army, where he can't escape by the simpler way.

An intelligent and pleasing woman was dissatisfied with her town and her husband. She referred to the former as "a piffling little place," and said of the latter, "He gives me no satisfaction." What was the solution? Recently she spent four months in New York, and with bright eyes and a pleased smile said, "You bet I had satisfaction there." Last winter she visited Los Angeles with the same gratification. Did she have a neurosis? Why should she? There was absolutely no conflict. She was as simple and direct as a child.

Contrast the following:

A woman of 34 years complained of daily headache, poor sleep, ready exhaustion, some dyspnea on exertion, poor appetite and constipation. With considerable pains, I ascertained that she too was dissatisfied with her husband and with her social and financial position. She could not adjust herself to conditions as they were, and she could not change them. Her ideals and training did not allow the simple means of escape adopted by the other. Instead of deliberately going to New York and California, she subconsciously went to headache and insomnia.

NEUROSIS AS DEFENSE REACTION

In short, the neurotic is an individual in trouble with no easy and direct means of escape. A neurosis is a defense reaction, a means of escape; a psychologic dugout in which to hide. That the difficulty may be imaginary, the patient fleeing from a ghost, does not alter the situation. His efforts to adjust his appetites and desires to the

demands of convention, society, the herd are the same as ours. He attempts to dodge defeat and to shift responsibility for lack of success as do we whom a lenient society calls normal. Because he played so poorly, an irascible golfer first threw his bag of clubs and then his caddie into the creek. Very, very often the nervously inadequate person unconsciously shifts the responsibility to some bodily trouble, when he naturally comes into the physician's domain. And too, too often the physician takes his complaint at its face value. Sometimes the literalness of physicians is equal to that of religious fanatics. Once I examined a justly celebrated clergyman who was in a state of profound delusional melancholia, in consequence of which he falsely accused himself of sundry grave sins. Having recovered, he was tried by a church tribunal and dismissed from the ministry because of these self accusations of a disordered mind. Such superficiality and narrowness makes a physician smile. But compare the following:

A young man brought to me his wife, who at various medical hands had received sundry powders and potions for insomnia, nervousness and loss of appetite. After a bit of questioning, I sent the husband on an errand. As the door closed behind him I said, "Now, quick, tell me what's the matter." The startled wife then told me that their young priest, a close friend of the husband, was almost daily assailing her virtue, and that she was quite distracted between fear that she might yield and fear to tell her husband.

And the following:

A woman of 50 years was having a prolonged rest cure because of general nervousness, mental depression, "exhaustion," and insomnia. She appeared to be very weak, and walked across the room with difficulty. A bit of direct questioning revealed that she was intensely afraid of a stroke, and that this fear was based on tinnitus, which she expressed as a "noise in the head." This to her meant cerebral calamity: a stroke, paralysis, death. When the simple situation was explained to her she got up and went to the coast of Maine for a holiday.

Would these medical examples make an ecclesiastic smile? The following incident is not unusual:

Many years ago, only with uncomfortable persistence did I dissuade a well-known surgeon (since deceased) from performing a gastro-enterostomy on his wife. He insisted that she never could be well until operated on. But I knew of grave emotional stress of which he was partly ignorant and which he partly ignored. With the mental adjustment which came about in a couple of years, all abdominal symptoms disappeared, and she has continued well.

How many of us constantly keep in mind that we, the acme of civilization and culture, have every instinct and passion of the caveman? Are we always alert for the ever present emotional-ideational-

intellectual conflict? And do we recognize its importance? To repeat: The product of these conflicts is WE — the patient himself. And in the vast and intricate complexity of modern life, the name of the conflicts is legion. Neurotics are just as different as physicians, and for as many different reasons. Consequently, investigation in many directions is necessary. Here laziness, carelessness and false modesty on the part of the physician have no place. I should not like to say, even if I knew, how often to my question "Did you tell all this to all these other doctors?" the reply has been "No, they didn't ask me."

THE SEXUAL ELEMENT

And here I venture a direct word on sex matters. Without following the self-styled psychanalysts in tracing practically all psychoneuroses to a sexual origin, without even discussing their tenets, I wish definitely to state that something relating to matters sexual has a great deal to do with starting many nervous disorders. Aside from the demonstration of experience, a little reflection will show that this is reasonable. In the present state of society, practically every individual between early childhood and presenility has sexual problems and conflicts. In the solution of the problems and disposition of the conflicts, generally he has the assistance of neither publicity nor knowledge. On the contrary, he is handicapped by ignorance, superstition and isolation. All the conditions are there for the development of fear, shame, remorse, guilt, resentment, a feeling of inadequacy or impotence; the most painful emotions, plus secretiveness. Who would not escape from them by way of a neurosis, very distressing but with none of the tragedy of the other forms of suffering? Thousands of soldiers escaped from the shell torn trenches, that is, from their intolerable emotions, by way of a psychoneurosis. Millions of us have tried to escape from other tearing emotions by means of so-called functional nervous disorder. Hence, whatever our decision as to the psychology of sex, in the case of the individual patient there is but one answer: sufficient investigation, proper instruction, and counsel based on adequate understanding.

But I do venture to add that, in my opinion, to express love of power, money and ease; fear of pain and death; the satisfaction of food, delights of the eye and ear; the disappointment of failure, the pleasure of work well done, all in terms of sex—howsoever sublimated—is to express a narrow conception of *Homo sapiens*. And I also

believe that in the vast majority of cases, the exhaustive and intricate corkscrewing methods of the freudians are unnecessary. Sometimes they are harmful.

DIAGNOSES THAT FALL SHORT

Our medical affinity seems to be the concrete and tangible. Organic abnormality is the most facial explanation of disorder. Given almost any complaint, if the patient reveals undoubted organic disease, our tendency is to stop there. When shall we learn that a prolapsed kidney or stomach may be as good as normal, a valvular lesion innocuous, a urethral stricture of small importance, a deviated septum symptomless, and a torn cervix not even a cosmetic offense? But prolonged fear, disappointment, resentment, anxiety, regret, perplexity are never symptomless. The physician's wife, mentioned above, undoubtedly had enteroptosis; but that did not cause the trouble. The following is a common type:

A middle-aged woman had been operated on for ruptured perineum, rectocele and "ulcer of the womb"; later, for hemorrhoids and laceration of the cervix. Still later, she had a curettage, and then the ovaries and tubes were taken out. Finally a hernia, a relic of one of the previous operations, was repaired.

No very exhaustive investigation was required to show that this patient never had been physically disabled, but that she always had been intellectually and temperamentally absolutely unequal to life's demands. Each operation was only an additional urge into physical invalidism as an escape from the toil and responsibilities that fell to her lot. That such treatment tends to perpetuate the trouble is obvious. If dysmenorrhea and pelvic pain are really a recourse from laborious housekeeping, ventrifixation fixes the mental attitude of the patient. And the next operation for adhesions makes her more adherent to her disability.

When a women dates her symptoms from marriage or childbirth, it behooves the physician to look for the presence of discontent, unhappiness and fear. A diagnosis of pelvic disease may have to be changed to mother-in-law, which often makes a more or less inadequate daughter-in-law. When a man is disabled by an organic disease or abnormality that apparently doesn't measure up to the disability, one should take the precaution to look for the neurosis which really makes the trouble. A simple arthritis, with which some people would happily limp through life, makes others useless. Why? Because there is

something back of the arthritis; something the matter with the patient himself. While the clinical picture may be made up of symptoms strictly organic plus others purely functional, the latter may be by far the more important, even though the former are more salient.

EFFECTS OF FEAR

Elsewhere,[1] I have tried to emphasize the importance of recognizing fear. One might think that if a patient were afraid he would know it and tell of it. Neither may be the case. That one may be sick from fear and not be aware that he is afraid is certainly true. And "to deny fear seems to be almost as instinctive as that emotion itself."[1] That is to say, the physician must not wait for the avowal: he must dig it out. This is especially true of that exceedingly common apprehension, the fear of losing the mind. Patients will carry this fear for years and never mention it. A very common way of consciously or unconsciously dissembling fear is to complain of the symptom which is the basis or the result of the particular fear. The patient bitterly complains of headache. But the real distress is not the headache (often it isn't a pain at all), but the idea that the headache means insanity or a stroke. Abdominal distress may be trifling, but it is disabling because to the patient it signifies cancer. But he doesn't say so. He hardly knows that it is so. He doesn't wish constantly to be afraid of insanity or cancer; he prefers to have headache or nausea. How can one successfully treat such a headache or stomachache without becoming acquainted with the patient himself?

FREQUENCY OF MILD MELANCHOLIA

One other very practical aspect of the real patient, the patient above the eyebrows, I must at least mention: the frequency of unrecognized mild melancholia. Instinctively, these patients hide their feelings of uselessness and hopelessness, their self reproach and fear of insanity. They complain of what to them seems to be the cause of their ill feeling, and generally this is some bodily complaint. Headache, insomnia, indigestion, constipation, biliousness; exhaustion from overwork, worry or sexual irregularities; leukorrhea, loss of memory and pelvic distress are among the more common. And the literal physician overlooks the disorder of the personality. The result is useless or

[1] Patrick, H. T.: The Factor of Fear in Nervous Cases, J. A. M. A., 1916, 67, p. 180.

harmful treatment. This is bad enough. What is worse, the patient is given every chance to commit suicide — which he rather frequently does. In Chicago there are more than 600 suicides a year, and I am quite sure that fully 400 of these are due to melancholia — every one of them preventable.

EFFECT OF DISTURBING EXPERIENCES

The relations of past experience to present conduct are most complex. Our feelings and behavior today are the result of myriad experiences, most of them forgotten, and still more not in our awareness at any given time. No man can trace all the steps that have led him to be a Republican, or to dislike a certain person. Why does Miss X delight in ice cream, and abominate pork chops? It didn't just happen. There are reasons. Of four men in trouble, one prays, one gets drunk, one has a fit and one has a headache. Why? That is for us to find out. Generally, it can be done. Not always.

Clinically, the relation of a pathogenic experience to consciousness is generally one of two, with no definite line of division. First, the patient remembers perfectly well the (generally unpleasant) experience, but has no idea that it has anything to do with his present trouble. Second, the disturbing episode has been quite forgotten and is brought back into consciousness only by some unusual stimulus or mental state. Obviously, it may happen that we cannot bring it back at all. To illustrate the first type:

A young traveling man was unable to eat in restaurants because of intense feeling of prostration and oppression, palpitation, etc. He had not in any degree forgotten that a few months before consulting me, he had been taken very ill while dining in a restaurant, had nearly fainted, and had liberally distributed vomitus over the floor before he could get out. But apparently, a connection between the causative disagreeable episode and the neurosis never had occurred to him, and information of the illness was not volunteered. It was elicited by leading questions.

Another example:

A middle-aged, happily married woman complained of nervousness, insomnia, mental depression, intense dislike of social intercourse, even with good friends, and intense agoraphobia. Painstaking inquiry for more than two hours, evidently with the cooperation of the patient, failed to elicit a cause. Only after the analysis of two dreams by Dr. Lewis J. Pollock, my assistant at that time, did we learn of events in her childhood and youth causing poignant shame and self reproach that were clearly the cause of her disorder. These experiences

she had not forgotten; but their relation to her present complaints had never occurred to her, the subject was distasteful, and instinctively, scarcely deliberately, she had suppressed the facts.

An example of the second type:

A young married woman had so-called vaginismus to a degree entirely preventing intercourse. No local cause could be found. The patient neither feared nor objected to the nuptial embrace; indeed, she was most anxious to be a complete wife and an early mother. It was only after many questions and the awakening of many associations that she recalled two not very striking experiences when she was about 11 years old. Aside from temperament, these were the prime cause of her disorder; but apparently for years she had not consciously thought of them.

NEED OF APPROPRIATE TREATMENT

A good many years ago, Möbius described akinesia algera, paralysis from pain; the patient does not move because it hurts to move. When we come to therapeutics for the patient himself, many of us have a sort of amblyopia algera. We do not see because it is uncomfortable to see. It is much more comfortable to say, "nothing to it," "just a nervous crank" and do nothing, than it is to realize that here is a pathologic condition, obscure, may be complex, that must be laboriously worked out. So we naturally go blind, see nothing and do nothing. Probably every physician makes an effort to regulate the bowels. How many of us make an effort to regulate emotional and intellectual movements? But intestinal stasis is vastly to be preferred to intellectual stagnation: so-called autointoxication is not half so lethal as disintegrating emotions.

To state it another way, we must first have a just conception of the nature of the trouble and then institute *appropriate* treatment. Nowadays few ovaries are removed for dizziness and indigestion, but the "rest cure" is applied about as heedlessly as was formerly oophorectomy. Confinement to bed, isolation, forced feeding and massage for perturbations of the personality may be compared to a linseed poultice for pain in the belly. Occasionally the cataplasm suffices, but treatment of the cause is to be preferred. Equally, we should treat the cause of neurotic manifestations. Who would prescribe a pill for vagrancy or a powder for prostitution? The tramp and the prostitute are recognized as defective, unadaptable to society as now constituted, except on the underworld level. The psychasthenic (nearly always miscalled neurasthenic), the neurotic, the psychotic is a rather similar product. Unadapted to the upper strata of social efficiency, he gravi-

tates to the underworld level of pain, prostration and dyspepsia: the realm of consultation rooms, hospitals and sanatoriums. But I hasten to add that when properly adjusted to his environment, the neurotic may be one of the most efficient, valuable and delightful members of society.

A fine young woman was about to decline marriage because handicapped, even disabled, by what she did not recognize as phobias. For years she had been unable to go down town except in a carriage, and then only for a few minutes. To go alone to a nearby market was out of the question. Deeply religious, she could not go to church alone, and when accompanied, she could sit only near the exit. There were other phobias. A short course of training and reeducation removed the lot, and for about ten years she has been an ideal wife and mother.

A fine young chap of 22, because hypersensitive and hyperconscientious, became depressed and worried over the usual sexual problems of youth to the extent of total disability. The situation was explained to him: in a proper environment, he was carefully guided and was gradually led back to normal activities. In the spring of 1917, he entered the army and served brilliantly thoughout the war.

An unmarried woman of 29, doing office work, for ten years had had attacks of dyspnea and palpitation, great weakness and insomnia. Although she positively and honestly denied that she was afraid of anything, exact questioning showed that she had several intense phobias. She really was ill and had been for ten years. But the trouble was not the heart muscle, it was lack of adjustment to her job, her associations and necessary conditions of living. Fortunately, she married happily, and her bodily complaints all disappeared.

A woman of 32, of the intellectual type, had been an invalid for years. Accurately to describe her symptoms would require a descriptive catalogue. They included "stomach trouble," "rectal trouble," severe headaches, ready exhaustion, tenderness at places over the abdomen and in the pelvis, loss of weight and anemia. She certainly had enteroptosis, with the right kidney far down. One of the greatest surgeons of Chicago thought it best to take out the appendix, fasten up the kidney, ventrifix and curet the uterus. Did all this help? Not a bit. She was sent East for a prolonged rest cure under the greatest master of that procedure, with the same result. She remained the same practically useless martyr, a burden to herself and the despair of her family. Finally, she was induced to take up an active, intellectual and taxing occupation in an environment that fitted her. Presto! The baffling organic disorders, the profound prostration, the disabling pains evaporated. She had found her place, and she has continued to be a busy, exceedingly useful and happy woman.

The following case shows the obverse mechanism:

A young man of ample means, shy and a bit effeminate, retired to a small farm where he raised a few fancy sheep and experimented in crossing flowers — all to his complete satisfaction, and he himself in perfect health. Circumstances forced him into business and the hated city. He developed rebellious stomach trouble, insomnia and headaches, lost considerable weight and frequently his temper.

NATURE OF THE TREATMENT

These illustrations, which might be continued indefinitely and with interesting variations, serve to indicate not only that the neuropath may be useful but also what sort of treatment he should have. Very simply stated, the object is so to mold the patient that he will fit his environment, and so to arrange the environment or so to place the patient that the environment fits him. Sometimes it cannot be done. Our laws and customs contain fragments from the dark ages and more primitive eras. So do we. Some of us belong to the period about 100 A. D. For such, transplantation to the present epoch is difficult. A few of us belong in the stone age, and we cannot live in the captivity of modern civilization without falling ill. Perhaps occasionally one is 500 years ahead of his time. If so, he has a hard life, and probably is a failure, judged by our standards.

In assisting to adjust a patient to necessary conditions, frequently we have to show him that he can do things that he says he cannot do. That is his way of expressing his great reluctance to do or fear of doing something necessary for his health. Demonstration discounts admonition. He should be given an understanding of his situation; but simply telling him is not enough. We must demonstrate to him that he can eat turnips or walk a mile or sleep without a hypnotic, or go without a headache powder.

Let me again emphasize that the headache or the pain in the legs or indigestion is simply a means of escape from something for which the patient feels himself inadequate, or really is inadequate. Our job is to make him equal to the task he is trying to escape or so modify the task that he can perform it, or give him another which he can do with satisfaction. To say, "Don't worry" or "Why worry?" or "That headache isn't in the least serious" is not enough. The unwholesome ideas, the distressing disorder, can be driven out only by wholesome satisfactory ideas, which in the vast majority of cases means a satisfying occupation, a something which makes life taste good.

THE OUTCOME

And for our encouragement, we may remember that the temperamental individual who is confused and discouraged by life's perplexities and takes refuge in physical disabilities is, when rightly placed, likely to be the finest enthusiast and the most glowing optimist. Just as he is

dominated and defeated by a depressing idea, so is he exhilerated and activated by sanguine ideas. Some of the greatest and most beautiful work of all time has been done by these men and women who are too much controlled by their emotions, too sensitive to the jars of a battling society, too unstable to carry the gross burdens of a materialistic world. Ours is the task, then, to strengthen their intellectual control, to toughen their shrinking sensibilities, and to modify their burdens. Thus may we, too, add to the sum total of human health, happiness and progress.

25 East Washington Street.

NEWER ASPECTS OF NUTRITION

E. V. McCollum

Professor of Chemical Hygiene, Johns Hopkins University, Baltimore

Nov. 24, 1919

Much has been accomplished in developing preventive medicine as a science, but activity in this field has in great measure been restricted to attention to the purity of the water supply, to sewage disposal, general sanitation, food inspection and the prevention of food adulteration. It is now well recognized by all progressive public health workers that education of the public in the principles of correct living, and the periodic medical inspection of all persons, notwithstanding the apparently healthy condition of many, constitutes the next, and in many respects the most important, line of advance. Such a plan will go far toward remedying defects before they become serious. Thus the tendency of today is toward doing preventive medical work with the individual as well as with the community.

There is another phase of the problem of prolonging the life and period of productivity of man which is not as yet very popular with the medical profession, but which has aroused the enthusiastic hopes of several investigators who have had the opportunity to make extensive observations of the effect on animals of diets similar in chemical composition. I refer to the prospect of planning the diet of the individual from infancy to old age so as to induce the optimum of nutrition. It has been thoroughly demonstrated that by proper diet much more can be done to promote health and to maintain the characteristics of youth than has been hitherto supposed.

We do not yet know with certainty why it is necessary, as general experience indicates, that man should become senile and die. The studies of Maupas and of Woodruff show that certain lowly organisms are capable of reproducing endlessly without conjugation. They prove that certain types of protoplasm are essentially immortal.

In the higher animals whose bodies are made up of a multitude of cells representing several types of specialization, the problem of nutrition and of eliminating the waste products of metabolism is more complicated than in the simple organisms, and is fraught with greater hazard to the individual. Each of the glandular tissues in these must assume the duty of working for other tissues. The digestive glands must functionate far beyond their own individual needs in order to

prepare food for the other tissues of the body. The kidneys must come into intimate contact with and secrete into the urine the metabolic end-products of a mass of protoplasm a hundred or more times their own bulk, as well as their own. The variable but more or less constant stream of foreign and more or less harmful substances formed in the lower intestine through the agency of micro-organisms must likewise pass through the kidneys. It has long been believed by Metchnikoff and others that the latter factor is one of great significance in causing damage to the tissues of the body and of contributing to early deterioration.

The tendency toward over-fatigue of certain of the more important tissues through the necessity of working for others as well as for themselves cannot be avoided beyond a limited degree. Reduction to a small fraction of the usual degree of injury that may result from the generation of foreign and toxic chemical substances in the digestive tract can, however, now be occomplished.

The adjustment of the protein intake to meet the requirements of the body, and at a level such that any benefits that may result from its stimulating qualities are gained, but not sufficiently high to cause the detriment which all agree results from surfeiting with protein food, doubtless forms one of the important factors in the preservation of vitality and health. There are several factors concerned with the plane of protein intake that we do not well understand, but considerable is now known about this phase of nutrition.

Modern research has shown that the relationships among the inorganic elements that are essential for the normal functioning of protoplasm form a much more important factor in growth and longevity and in consequence well-being than had hitherto been supposed. Even the difference between the calcium, sodium and chlorin contents of certain classes of our most important natural foodstuffs is sufficiently great to determine whether or not growth can take place. Although our knowledge of the details of this important question is still rather meager, some of the more easily regulated ones can be controlled in ordinary practice to the advantage of man and animals.

In the popular mind, the most attractive feature of the subject of nutrition during recent times is the spectacular effect of the lack of a sufficient amount of one or another of at least three chemical substances whose existence was not suspected a few years ago. The dietary deficiency diseases, scurvy, beri-beri and xerophthalmia of a

certain type, result from specific starvation for one or another of these substances. The optimum amount of these substances in the diet cannot be stated in the light of our present knowledge, but the content of each of them in certain of our more important foodstuffs is sufficiently well known to render it possible to plan diets so as to guarantee a reasonable degree of safety.

Animal experimentation has shown that there are great differences in the biologic values of the proteins derived from different sources. This difference depends on the fact that the proteins in different foodstuffs yield varying amounts of the amino-acids or digestion products. If the yields of the several amino-acids is such as to make possible the efficient transformation of food proteins into tissue proteins the proteins have a high value. If, however, one or more of the amino-acids is present in such small amounts as to make it impossible to utilize the more abundant amino-acids, they form the limiting factor that determines the value of the protein in nutrition. Many of these digestion products are indispensable in the diet, since they cannot be synthetically produced within the tissues. In considering the value of a natural foodstuff or of a diet consisting of a variety of substances, the idea of quality of protein enters into the calculations of the dietician of today,

Our knowledge of the great variation in the biologic values of proteins from various sources throws a new light on a possible source of injury to the body tissues. Excessive feeding of proteins is generally held to lay a burden on the organism because of the magnitude of the task of metabolizing the quantity of amino-acids absorbed. From what we know of the intermediate compounds formed in the catabolism of amino-acids, there can be little doubt that some are a physiologic abomination, and dealing with them by the glandular structure is not without a degree of unfavorable effect that in time produces visible alteration in their functional capacity. It seems logical to assume that physiologic well-being will be best promoted by the employment in the diet of proteins so constituted as to be transformable with little waste into tissue proteins.

The best chemical analysis of a foodstuff which the chemist is able to make determines the amounts of protein, carbohydrate (starches and sugars), fats and oils, and mineral salts that it contains. For more than thirteen years it has been known, however, that when a mixture of these substances, each carefully purified, is fed to a young animal the latter cannot grow, or live long. The reason was very difficult to

Explanation of Plate I

Chart 1.—Lot 417 shows the results of restricting young rats to a diet of purified protein, salts, carbohydrate and agar-agar, together with an extract of a natural foodstuff that furnishes the dietary factor, water-soluble B, the substance which prevents beriberi. The diet was complete except for the absence of the fat-soluble A. As a rule, there develops in animals so fed, a type of xerophthalmia, which is due to the lack of the fat-soluble A. When a fat or other natural food rich in cellular structures (as contrasted with reserve food materials), is added to a food mixture of this type, the resulting diet becomes capable of inducing growth.

Lot 418, period 1, shows the curves of body weight of rats fed a diet similar to that described above for lot 417, but differing in that it contained butter fat (fat-soluble A) but lacked the extract of natural foods, and, therefore, contained no water-soluble B. On this diet xerophthalmia does not develop, but the animals ultimately lose muscular control and manifest symptoms suggestive of beriberi in man. Growth is not possible on this diet, but everything which is needed in the diet so far as chemical analysis could show, is present.

These results show the necessity of a biologic analysis of foodstuffs. Growth at once took place when, in period 2, the dietary essential water-soluble B, which is likewise soluble in alcohol, was added to the diet. This dietary factor is abundant in all natural foods. In investigations of the nature of those here described, it is usually added as an alcoholic extract of a natural food.

Lot 419 shows the type of growth curves secured with diets containing both fat-soluble A and water-soluble B, in addition to the long recognized food substances, protein, carbohydrate, fat and a satisfactory supply of the inorganic elements essential for the nutrition of an animal. There is much reason to believe that each of the two unidentified dietary factors A and B contains but a single chemical complex which is physiologically indispensable, and not a group of such substances.

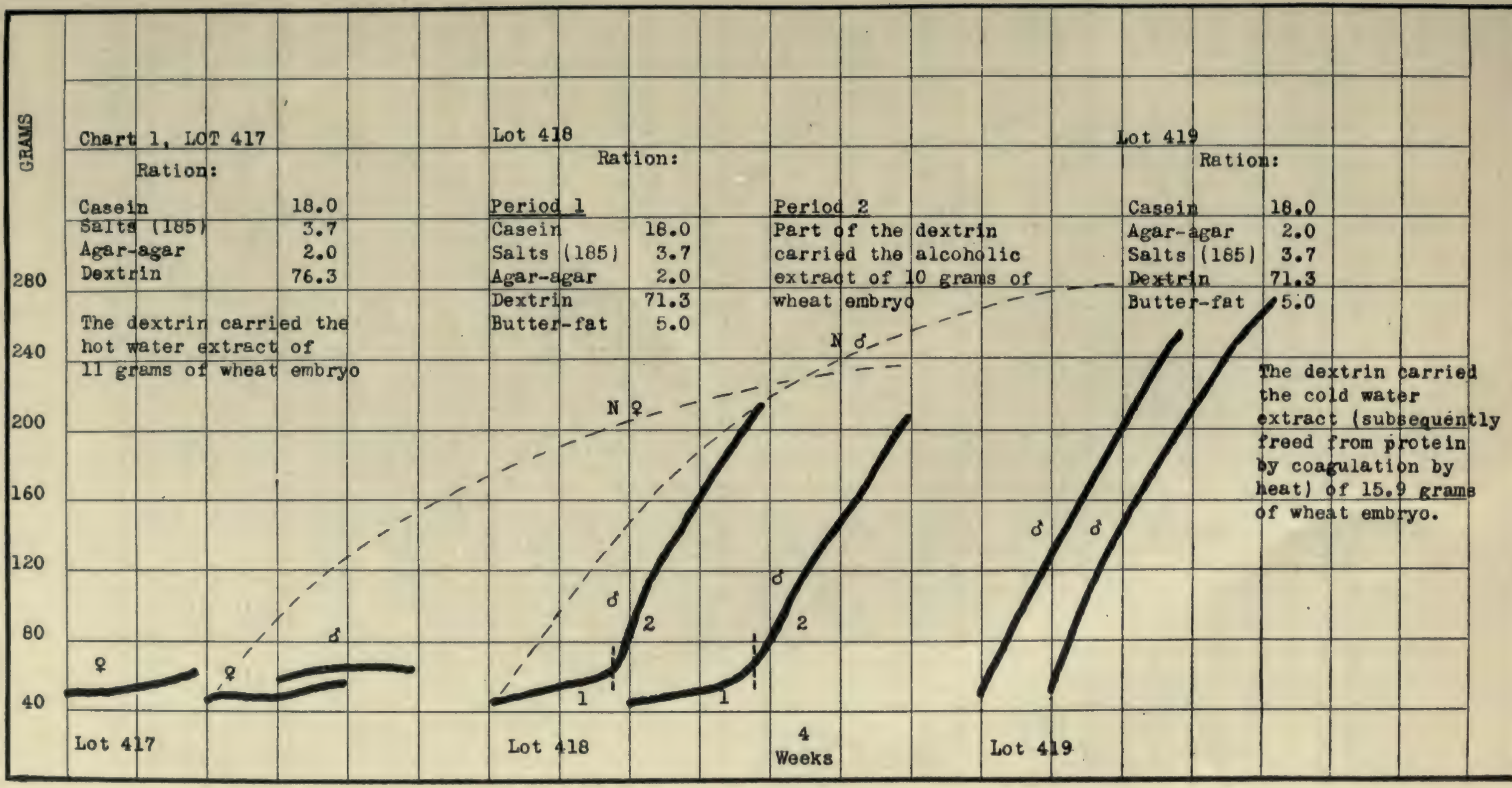

GRAMS
280
240
200
160
120
80
40
Chart 1, LOT 417
Ration:
Casein 18.0
Salts (185) 3.7
Agar-agar 2.0
Dextrin 76.3
The dextrin carried the hot water extract of 11 grams of wheat embryo
Lot 418
Ration:
Period 1
Casein 18.0
Salts (185) 3.7
Agar-agar 2.0
Dextrin 71.3
Butter-fat 5.0
Period 2
Part of the dextrin carried the alcoholic extract of 10 grams of wheat embryo
Lot 419
Ration:
Casein 18.0
Agar-agar 2.0
Salts (185) 3.7
Dextrin 71.3
Butter-fat 5.0
The dextrin carried the cold water extract (subsequently freed from protein by coagulation by heat) of 15.9 grams of wheat embryo.
N ♀
N ♂
♀
♀
♂
♂
♂
♂
♂
1
2
1
2
Lot 417
Lot 418
4
Weeks
Lot 419

PLATE I

ascertain, for it is due to the lack of certain substances of a moderately unstable nature, the existence of which was not suspected. Certain species of animals, such as the rat, appear to require, in addition to the long recognized dietary complexes, but two of the unidentified dietary essentials. The most common designation of these is perhaps the term "vitamin" which includes fat-soluble A and water-soluble B. No less than twenty-five names have been invented for these substances. Other species of animals, such as man, guinea-pig and monkey, require three, the additional one being called water-soluble C. These terms have been applied provisionally pending the discovery of the chemical natures of these interesting substances. The importance of each of these substances in the diet of the rat is illustrated by the curves in chart 1.

It has been abundantly demonstrated that for satisfactory nutrition the mammal requires nine mineral elements in addition to the essential organic complexes, in order that its diet may be adequate. These are calcium, magnesium, sodium, potassium, chlorin, phosphorus, sulphur, iron and iodin. These can be supplied in the form of inorganic salts except in the case of sulphur, which must be contained in the diet in the form of the sulphurized amino-acid cystine. It is doubtful whether there is an order of relative importance among these, for it appears that all are indispensable. There must be present in the diet either glucose or a carbohydrate which can be converted into glucose in the body. Cane sugar, glucose, beet sugar and the starches serve this purpose.

It seems highly probable that fats and substances closely related chemically to the fats are entirely dispensable in the diet. Up to the present time it has not been found possible to nourish an animal properly with a diet free from this class of compounds because one of the unidentified dietary essentials is associated only with certain fats. Therefore, in working with a diet made up of purified foodstuffs it has been necessary in every case to add one of these fats, not because of the fat itself, but because of the presence of an unknown substance (fat-soluble A) which is contained in it.

It is interesting to consider the distribution of the three unknown substances that the diet must contain. The substance fat-soluble A is found in butter fat and egg yolk fats, and in the fats from the interior of the cells of the glandular organs of animals (e. g., the liver and kidney) in greater abundance than in any other foods. Leaves of plants constitute the next important source. The seeds, tubers and

fleshy roots are all relatively poor in this substance. It has been suggested that among the latter those which contain yellow pigment are richest.

The water-soluble B dietary factor is widely distributed among natural foodstuffs. The only common foods lacking in it are polished rice, the sugars and starches, and the fats and oils from both animal and vegetable sources. Food containing small quantities of it are: white flour, degerminated cornmeal, macaroni, spaghetti, and other products prepared principally from bolted wheat flour. All whole seed products, tubers and fleshy roots, leafy foods, milk and eggs contain it in relative abundance. Muscle cuts of meats are very poor in it, but the glandular organs contain it in abundance.

The water-soluble C is abundant only in fresh vegetables, fruits and fresh milk from cows in pasture. Cooked and dried foods have in great measure lost their peculiar dietary properties with respect to this substance.

The effects of specific starvation from one or another of these three substances are of special interest. Each of them is necessary in the diet in order to prevent the development of a specific syndrome that we call collectively deficiency diseases.

One of these, which is caused by a lack of fat-soluble A in the diet, is characterized by a change in the eyes, in which edema, inflammation, and in some cases perforation, are the most important. Much remains to be learned regarding the histology and pathology of starvation for this dietary complex. Without it growth is impossible, and death soon intervenes. There is much evidence that a lack of a sufficient amount of fat-soluble A is one of the factors associated with the etiology of rickets.

A lack, either relative or absolute, of the second dietary factor of unknown chemical nature, water-soluble B, leads to the development of a condition of polyneuritis which in man is known as beriberi. Paralysis is the most striking general feature of the disease.

The third of the dietary complexes under consideration is that which prevents the development of the syndrome of scurvy. It is the least stable of the three. The antineuritic substance is the most stable.

For several years the three substances just discussed have in the popular mind overshadowed in importance the long recognized dietary essentials. It should be emphasized that there is no basis in fact for considering them any more important than the proteins or than any

one of the essential mineral elements. All are indispensable components of the diet, and are, therefore, of essentially equal importance. Any appraisal of the quality of a diet must include a consideration of the quality and quantity of protein; the content of each of the necessary mineral elements; the content of each of the substances concerned with the etiology of the deficiency diseases, and the availability of its carbohydrates.

After the factors which operate to make a diet complete and satisfactory were appreciated, a series of studies were carried out with a view to determining the nature and extent of the dietary shortcomings of each of the more important of our natural foodstuffs. In the light of these studies it has become possible to make certain generalizations of far-reaching importance in the nutrition of man and animals. On these observations is based a new type of classification of the vegetable foodstuffs depending on the function of the part of the plant from which they are derived.

It has been found that all those parts of plants that have the functions of storage tissues, viz., the seed, tuber and fleshy root, have remarkably similar dietary properties and similar shortcomings. Notwithstanding the great difference between the legume seeds, such as the pea and bean on the one hand and the potato or turnip on the other, they have very nearly the same dietary values in certain respects. All of the cereal grains, legume seeds, tubers and edible roots are deficient in some degree in at least three dietary factors. All contain proteins of relatively poor quality; all contain too little of certain mineral elements, especially calcium, sodium and chlorin, and all are deficient in fat-soluble A. As stated above, there may be a few exceptions to the latter generalization in the case of certain yellow pigmented roots.

The leaf of the plant possesses very different dietary properties from the seed. The palatable leaves are alone a complete food for those types of animals that have digestive tracts sufficiently capacious to enable them to eat a sufficiently large amount to meet their energy requirements. This superiority in dietary properties correlates with the special function of the leaf as contrasted with the storage tissue, such as the seed, tuber or root. The leaf consists of actively functioning protoplasm supported by skeletal tissue. It is the seat of the synthesis of proteins, carbohydrates and fats. It is the seat of active respiration and metabolism. The seed, tuber and fleshy root represent on the other hand packages of reserve food materials, with a few living elements.

In general the structures of the storage tissues do not contain all the complexes necessary for the construction of living protoplasm, and are accordingly incomplete foods.

A similar parallel between function and dietary properties can be drawn in the case of the highly specialized muscle tissue on the one hand and the actively metabolizing glandular tissues on the other. The muscle tissue has dietary properties almost identical with the seed, tuber or root in all respects except its richness in protein. It lacks calcium, sodium and chlorin, fat-soluble A, water-soluble B and water-soluble C. The glandular organs, such as the liver and kidney, are much more complete foods. Indeed, they have all the complexes that are essential for the construction of living tissue, and when supplemented with certain salts, a carbohydrate, such as starch, approximate much more nearly a complete food than would a similar amount of muscle tissue with starch.

Since there are closely similar dietary properties in the storage tissues of plants and of muscle tissue of animals, it should be expected that mixtures of these even in considerable numbers should not form satisfactory diets. In many feeding experiments this has been shown to be the case. Although it is possible for a young animal to grow on a seed, tuber, root and muscle cut of meat diet, its growth is never normal in rate or extent. It will always be stunted, and will fall below the normal standard of performance in reproduction and rearing of young, and in span of life.

Consistently unsatisfactory results have been secured on diets consisting of wheat flour, cornmeal, rice, peas, beans, potato, turnip, beet, rolled oats and round steak. The round steak was included to the extent of 10 per cent. of the dry matter of the diet.

This leads us to a consideration of diets that succeed in the nutrition of animals. In an extensive inquiry, covering 12 years, and based on nearly 4,000 feeding experiments, we have succeeded in nourishing animals in an approximately normal fashion with but 3 types of diets.

It is possible to select carnivorous foods so as to secure a fairly satisfactory diet entirely derived from animal tissues. Young animals cannot grow or long remain in health when restricted to muscle tissue as their sole food. When blood, liver, kidney and other glandular tissues are selected, together with a certain amount of bone substance, the food supply is sufficiently good to lead to normal development.

Muscle tissue must be liberally supplemented with glandular organs to make possible success with the strictly carnivorous diet. The carnivorous diet has been used by man occasionally, the Eskimo and some American Indians being examples.

It has been found possible to supplement the seed, tuber, root and muscle meat type of diet with liberal amounts of the leafy vegetables and secure a fairly satisfactory diet. This requires a liberal supplementing with leaf in order to make good the deficiencies of the remainder of the diet. This type of diet is common among the Orientals.

The third type of successful diet is that derived from cereals, legume seeds, tubers, and fleshy roots, with or without meats, supplemented with liberal amounts of milk. Milk is so constituted as to make good all the deficiencies of the classes of foods just enumerated.

It is so important to appreciate the special qualities of the leafy vegetables and milk that I have been accustomed to designate these as the protective foods. They are protective because they are especially rich in those elements and complexes in which the storage tissues of plants and muscle tissue are poor.

I will now consider the application of the facts discovered through animal experimentation to human problems.

Various attempts have been made to account for the differences in achievement of man in the several parts of the world. Some investigators regard race as the most important factor and believe that certain races are naturally inferior to others. Huntington of Yale University attributes to climate the most important rôle in determining the efficiency of man in the several regions of the world. Numerous authors have emphasized the importance of a satisfactory diet for the maintenance of the health and of physical fitness, which all agree forms the fundamental basis of achievement. No one up to the present time has, however, been able to make a strong case in favor of nutrition as a factor; this is proved by the number of dietary systems and fads which have been offered to the public. While one enthusiast extols the virtues of abstemiousness, another warns against it and points to the high meat consumption of the successful nations of the earth. While thousands of dyspeptics adopt vegetarianism, others explain the remarkable health of centenarians as being due to the bacillus of sour milk. The pronounced difference in the value of a food mixture consisting of cereal products, tubers, roots, legume seeds and steak,

with and without milk, is shown in chart 2. Careful consideration shows that the more advanced peoples of the world are those who live on the vegetable and meat diet supplemented with milk and its products. The second class in respect to advancement and aggressiveness includes those that eat liberally of the leafy vegetables. All strictly carnivorous men live in climates that preclude the development of any high degree of civilization. They have nothing to strive for further than food, shelter and clothing, and do not accumulate much property.

There can be no doubt that there are carnivorous animals such as the lion, tiger and jaguar, that live in the hottest parts of the world, yet represent some of the best examples of physical development in the animal kingdom. Neither the heat, monotony or high temperatures, humidity or aridity can be said to interfere with physical development.

The tiger thrives among the wet estuaries of Bengal, and the jaguar in the hot and sultry forests of Brazil. The lion is equally vigorous on the margin of the desert. We can find no evidence that climate is a factor of any appreciable importance in the development of lower animals so far as physical well-being is concerned.

Huntington has made a very plausible case for climate as the most important factor in determining the efficiency of man in the different regions of the world. He points out that the changes in the condition of the weather so characteristic of the northern parts of the United States and lower Canada in the western hemisphere, and of England, northern France, Holland, southern Germany, etc., are the ideal conditions for stimulating effort, both physical and mental. This assertion he bases on careful observations on the amount of work of several kinds which workers accomplish in climates varying from that of Connecticut to that of Florida. Temperature he finds to be the important factor in determining the aggressiveness and ambition of the individual. The farther south one goes, the more uniformly warm it is, and the more the climate departs from the typical cyclonic stormy type so characteristic of the northern states and of England.

Huntington further correlates the character of the climate of Europe, Asia, Africa, and North and South America, with the state of advancement of their peoples, and finds a remarkable relationship between them. Monotony of climate over long intervals is said to be detrimental to achievement. He eliminates race as an important factor in determining the problem by pointing among other illustrations to the

Explanation of Plate II

Chart 2.—Lot 2,147 received a diet of wheat flour, cornmeal, potatoes, beets, turnips, peas, navy beans and steak.

In the absence of experimental demonstration no one would believe that this food mixture would fail to meet all the needs of a growing animal. The addition of a liberal amount of milk serves, however, to improve this diet in a remarkable degree.

Lot 2,148 was given the same food mixture as lot 2,147, except that 10% of whole milk powder (Merrill-Soule) replaced a part of the potato, peas and beans. The effect of this addition on the growth curve and span of life is indicated by a comparison of the two growth curves in chart 2. These rats each fairly represent a group of six animals in their experimental groups. Certain foods, such as milk and the leafy vegetables, are to be regarded as protective foods because they correct the faults of those common articles that enter freely into the diet of man.

The list of foods in the diet of Lot 2,147 can be combined in a typical menu as follows: broiled steak, baked potatoes, peas, pickled beets, bread, mince pie, coffee. While this menu is, if properly prepared, appetizing and attractive, and affords the extent of variety to which we are accustomed, it is deficient in certain respects, viz.: in the element calcium and in the unknown dietary essential that is most abundant in certain fats but not found in vegetable fats or oils.

This menu can be easily modified by the inclusion of milk to make it a much more satisfactory diet: broiled steak, mashed potatoes, creamed peas, buttered turnips, bread, lemon pie, coffee.

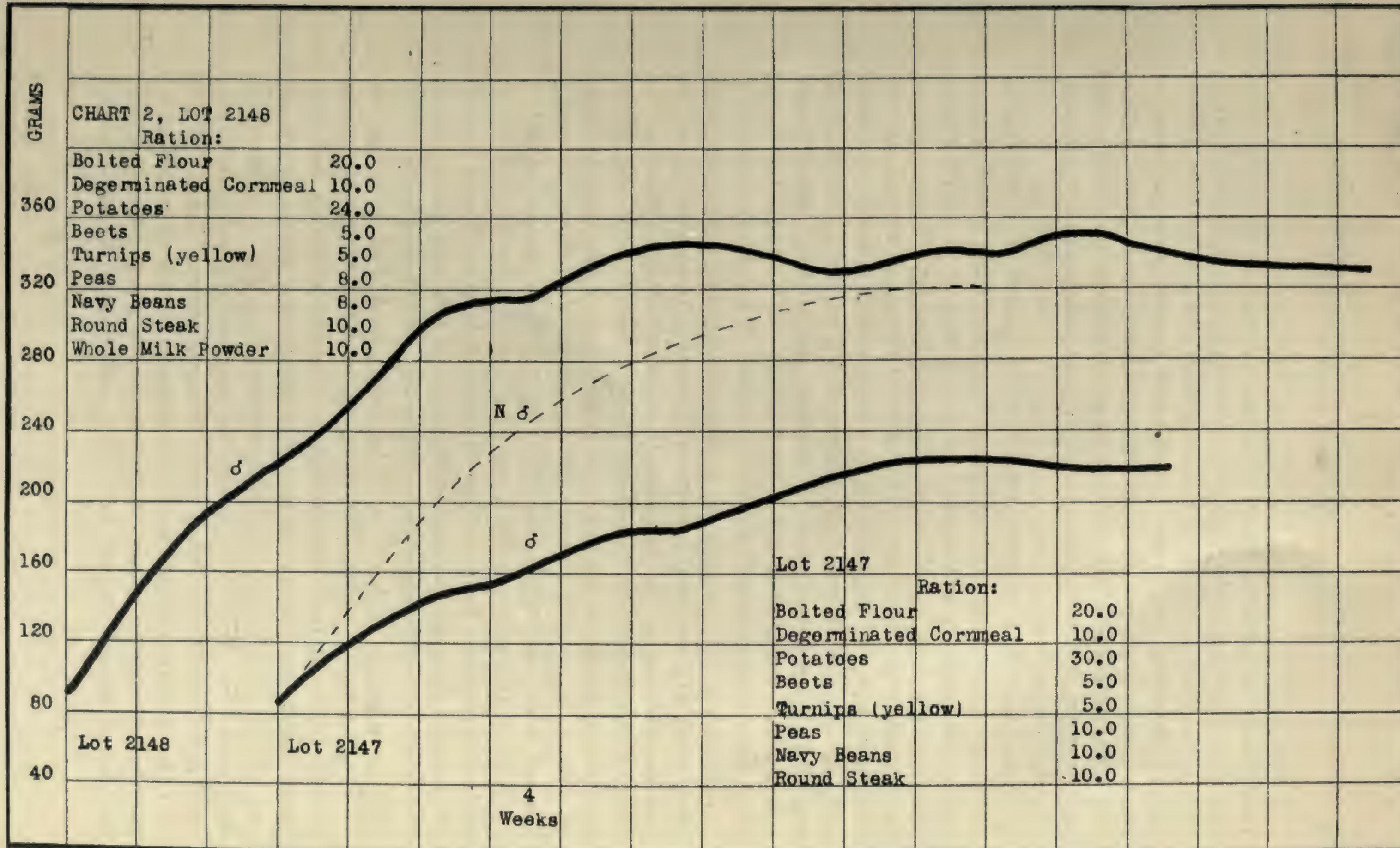

GRAMS
360
320
280
240
200
160
120
80
40
CHART 2, LOT 2148
Ration:
Bolted Flour 20.0
Degerminated Cornmeal 10.0
Potatoes 24.0
Beets 5.0
Turnips (yellow) 5.0
Peas 8.0
Navy Beans 8.0
Round Steak 10.0
Whole Milk Powder 10.0
♂
N ♂
♂
Lot 2147
Ration:
Bolted Flour 20.0
Degerminated Cornmeal 10.0
Potatoes 30.0
Beets 5.0
Turnips (yellow) 5.0
Peas 10.0
Navy Beans 10.0
Round Steak 10.0
Lot 2148
Lot 2147
4
Weeks

PLATE II

condition of the white people of the Bahamas, who are the descendants of virile Southern settlers, as contrasted with that of other loyalists who at the time of the revolution emigrated to Canada. The former have degenerated into "poor whites" who are too proud to work at menial labor in competition with the negro, and too shiftless to compete with him successfully. The latter are among the most prosperous and progressive citizens of one of the finest examples of a commonwealth in the world.

Huntington sees no great hope for the future of civilization in Asia, Africa or South America, because the white man, who is regarded as superior to the other races, degenerates in the enervating climates. The view is held that when the white man migrates to climates less stimulating than those of his original home, he appears to lose both in physical and mental energy. If it is true that under such influence man becomes careless of sanitation and of food, and thus secondarily becomes susceptible to diseases, then indeed there is little reason to hope that the dream of the hygienist can be realized, viz., that the tropics can ultimately be made the abode of a cultured population.

Plausible as is the correlation between climate and civilization which Huntington has constructed, it seems to me that another interpretation can be placed on all the data that he presents, which in the light of what we now know about the effects of diet on health, will come nearer the truth. In order to appreciate the importance of diet on the welfare of nations we should consider for a moment the effects of certain types of faulty nutrition on the life history of experimental animals.

When a full grown animal, such as a rat, is placed on a diet of seeds, tubers, fleshy roots and muscle meats, it begins to hurry through the span of life, developing the characteristics of old age at a rate double or more the rate observed in a well nourished animal. Such animals do not succeed well with the nutrition of their offspring, and die at a fairly early age. The young, if restricted to the diet of the parents, are never their equal physically, have poor success with their young, live a much shorter period than the species is capable of, and are subject to infections and abnormalities in a degree unknown in their ancestors. With each succeeding generation weaklings predominate, and the strain dies out within a few generations.

If we apply to the natives of the Bahamas the test of nutrition, we find that the diet is of such a character as to account for degeneration in considerable degree within the period since the islands were

settled by loyal Tories who were not willing to live under the Stars and Stripes. During this period they have depended for their food supply largely on citrus fruits, pomegranates, pineapples, bananas, melons, yams, potatoes, guinea corn and peas. This list, it will be noted, consists of fruits and other storage tissues of plants. It has been supplemented with a certain amount of animal foods, principally fish, although some muscle meats from mammals have been eaten. This type of diet, it will be remembered, is unsatisfactory for the nutrition of an animal over many generations, and leads to deterioration in the stock. This is the condition found in the Bahamas.

On the other hand, the people of Canada have lived essentially on the same type of diet as that employed in the northern United States. It includes all the products of field and garden with which we are familiar, together with meats in liberal amounts and dairy products in moderate quantities. The latter is the kind of diet that supports the civilization of England, and of the most progressive European countries as well as that of the northern United States, and all other parts of the world that have been peopled by colonization from European stock, wherever the climate permits.

Another example of the failure of health of Europeans largely as the result of restricted diet improperly selected is found in Newfoundland and Laborador. In both these districts occurs the deficiency disease beriberi, which is caused by lack of a sufficient amount of the dietary essential water-soluble B. The disease is the same that is seen so frequently among the poor laboring classes of the Orient who subsist largely on a diet of polished rice and fish with a few vegetables. The diet in Newfoundland consists, according to Dr. Little, of bread made from bolted wheat flour, tea, fish and salt meats, and raisins. A similar food supply is all that is available in Laborador.

There seems to be good reason to believe that a second deficiency disease actually occurs among the people of both of these regions as the result of their restricted and faulty diet. I refer to a condition popularly called night blindness, which is common, especially among men who are out at sea for a considerable period and are subjected to a fare of poorer quality than that obtainable at home. I cannot affirm that it is demonstrated that this is incipient xerophthalmia due to a lack of the unknown dietary complex found most abundantly in butter fat and a few other fats, but there is good reason to believe that it is. Night blindness occurs among men in lumber camps in Canada and

elsewhere, and the popular local remedy is to feed the patient milk or cheese. Prompt recovery is said to follow this modification of the diet. In these camps the food supply is frequently limited for considerable periods to bread, salt or canned meats and peas or beans. This again is a seed and meat diet, and has been found to be unsatisfactory for animals and for man. The same condition appears occasionally to be encountered in Japan, and is not uncommon in parts of India. In both these countries the popular remedy is the free use of liver as a food, and in India it is recommended that a poultice of liver be applied to the eyes as well. It is safe to say that it is the consumption of the glandular tissue that results in benefit to the eyes of the sufferer. In Japan eel fat and chicken livers enjoy the reputation of being efficacious in the cure of xerophthalmia. Night blindness is reported to be encountered in Russia somewhat commonly during the latter part of the Lenten fast. During this period the people restrict their diet largely to cereals, and fail to secure enough of the dietary factor which is concerned with the deterioration of the eyes.

According to the views of those who believe that climate in itself is the chief factor in determining progressiveness, it will never be possible for people in central Asia to develop a high state of civilization. It seems worth while to examine into the validity of this conclusion, and in doing so we must make clear what conditions we accept as a fundamental basis of civilization. If physical well-being as exemplified in excellent development, together with courage and energy, be the first requisite, we have in the past and have now some notable examples of it among the tribes of central Asia. In order to reach a high degree of civilization, however, it is necessary that a relatively high stage of mental development, together with both social and political fixity, shall be attained.

Of fundamental importance for the development of a highly organized society and a state of advanced civilization is the right kind of religion, since this determines the mental attitude of the individual toward his associates, his neighbors and his own destiny.

The Mongol hordes of central Asia in the thirteenth to the sixteenth centuries overran and conquered much of western Asia and Europe as far westward as the boundary of Austria-Hungary. Eastward they overran a large part of China, and to the North they were for generations a thorn in the side of the Russians. These Mongols, who played so prominent a part in history, were typical representatives of the sour

milk drinkers so common among the pastoral peoples of parts of Asia and eastern Europe. At the present time the natives of northwest Mongolia have many cattle, sheep, horses and camels, and derive their sustenance almost entirely from their flocks and herds. The Mongols had all the elements necessary for the creation of a high development of civilization except the mental attitude toward society that would permit them to respect the personal and property right of others. They had not the sense of honor and the appreciation of the ethical relations between man and man that are necessary for the establishment of a stable society based on law and order, and governed in the interests of the people. Such governments had not at that time gained popularity anywhere in the world. The frame of mind that makes possible these things can be attained only through the establishment of the best systems of ethics and religion. Climate has nothing to do with these.

It is significant also that the Chinese, while possessing a civilization of great antiquity, have lacked certain qualities that are necessary for the formation of a great nation. For many centuries they were overrun by successive waves of invaders from the northwest. The Chinese have always lived on a diet derived from cereals, legume seeds, tubers, fleshy roots and meats, together with a liberal addition of green leafy vegetables and some eggs. The widespread practice of sprouting grains preliminary to their use as human foods is justified by the results of modern science. The consumption of a large amount of leafy foods has, I believe, been a factor of the greatest importance in promoting their well-being, for as has been already mentioned, the leaf of the plant possesses dietary properties very different from those of the seed or other storage organ. These special properties are those that are necessary to correct the deficiencies of the seed, tuber, root or muscle meat type of diet. It is perhaps significant in this connection that the Chinese have, on their diet in which the leaf was almost the sole protective food, been unable to cope with their sour milk drinking neighbors to the northwest. The descendants of these waves of invaders still live in China, forming classes that have never been assimilated socially.

The ancestors of the present Turks were likewise a pastoral people and were sour milk drinkers. This constituent of their diet alone would suffice to make it highly satisfactory, and to insure, in the absence of contagious or of insect-borne diseases, an excellent physical development. Such a development is the essential basis of military ambition and success, and was possessed by both the Mongols and the Turks.

Almost every one is familiar with the conclusions of the famous Russian bacteriologist Metchnikoff, that the remarkable number of centenarians among the Bulgarian peasantry is the result of the ingestion of sour milk. Metchnikoff believed that the remarkable results of the regular use of their simple diet was due to the lactic acid producing organism which causes the souring of the milk. He attributed its beneficial effects to the production of lactic acid by this organism in the intestine, and the inhibition of the growth of the harmful putrefactive organisms which develop there in the residues of protein rich foods. He attributed the early aging of mankind and of animals to the absorption of these toxic products.

It is of more than ordinary interest that the most modern investigations in the field of nutrition, carried out by methods that far surpass those of the past in scientific accuracy, support his observations in a general way as regards the beneficial effects of the diet of the people he observed, but detract from the importance of the organism that the milk contains. It is the correction of the deficiencies of the types of diet that consist mainly of seed products, tubers or fleshy roots and muscle meats, by the inclusion of the protective food milk, which greatly improves health and increases vigor. The bacteria in the milk are of secondary importance.

The Arab of today is an example of the effects of a diet in which sour milk finds a prominent place. He is described by all modern writers as singularly handsome, tall and lithe, with beautifully molded limbs. Dwarfs, hunchbacks and misshapen persons are seldom seen in Arabia. Few races of humanity excel the Arab either physically or morally. The Arab derives his sustenance in great measure from fruits and milk. Most of the milk is soured, but this forms the most prominent constituent of his diet. In fact, under the names sheneena, leben, yohourt, keffir, koumiss, matzoon and dadhi, soured milks have been used from earliest times very extensively over a large part of central Asia as well as Egypt, Palestine, Arabia, Turkey and the Balkan States. Wherever fermented milks are extensively used as food the physical development of the people is usually good, and the length of life exceptionally long in many instances.

Huntington believes that the climate of China makes impossible the development of a highly progressive race. This does not seem justified without taking into account other factors that are of importance in

this connection. We must agree on what conditions are essential to the development of a high state of civilization before we can agree on other points.

In a sparsely settled country, where the care of flocks and herds is the only means of livelihood, as is the case over large areas of Asia, pasturage and water are likely to be greatly prized, and the rights to them sharply contested. Enmity between neighbors, lack of education, and the consequent lack of opportunity to gain ideas from others through reading, lack of incentive to do anything other than seek the protection of the animals that contribute to the comfort of man, are themselves reason enough for the lack of development of a high state of civilization. The climate need not necessarily be responsible for the result. The energy and aggressiveness of people who have dwelt in such regions have been repeatedly exhibited in wars of conquest. They have the physical development and intelligence necessary to form the basis of a civilization, provided the necessary conditions for its growth are existent.

It is necessary, in order that a civilization may develop, that food, shelter, clothing, and other comforts of life shall be obtainable without too great a drain on the physical resources of man. There are several reasons why these conditions are best fulfilled in the cooler parts of the temperate zones where the rainfall is most satisfactory for the growth of farm crops.

One of these conditions is that the winter in these regions destroys certain insects that would otherwise destroy the crops. Certain disease transmitting organisms, such as the cattle tick and the tsetse-fly, which bear respectively the Texas fever and the sleeping sickness, do not survive the northern winters, and the population in these regions enjoy freedom from these diseases. Cold winters limit the number of species of weeds and other obnoxious plants, and render the production of useful crops less laborious. These are factors of the greatest importance to agriculture and to the well-being of man.

Wherever insect life, such as the destructive ants of tropical forests or myriads of mosquitoes and other insects, detract from the comfort of man, and where rank vegetation renders futile his efforts at clearing ground for cultivation, and where diseases destroy his domestic animals, and place in his own blood disease producing organisms that rob him of his vitality and ambition, man must have recourse to power other than his own strength to overcome obstacles. If we give him the aid of

machinery and control over suitable sources of power to free him from his crushing burdens, and the aid of science to free him from the scourge of disease, and a diet that causes him to develop a high state of physical perfection, we may confidently expect of him any development of mental traits consistent with his heredity. It is the aim of those who direct the great agencies for the promotion of hygiene and public health to bring to the inhabitant of the Tropics these blessings. They have faith that these inhospitable regions can ultimately be made the seats of creditable human society. Not until all of these problems have been solved, however, will man succeed in the less hospitable parts of the world.

One not infrequently sees in discussions of this nature the statement that in warm regions, where food is easily obtainable, and little shelter or clothing is necessary to the comfort of man, he sinks into indolence, and remains in a state of ignorance and degeneracy. It is urged that only in such a climate as necessitates exertion and foresight during the summer in order to provide food, shelter and clothing with which to pass a severe winter in comfort, will man develop in a satisfactory way the higher virtues of civilization. The theory has been postulated that energy, aggressiveness, frugality, foresight, inventiveness, solicitude for dependents, respect for property rights and the other virtues of man in his most highly advanced condition, are best fostered in a climate that offers vicissitudes, and requires that the life of the individual shall be a struggle with his environment.

Others tell us, and it appears logical, that so long as man is forced to spend his days in a struggle for existence he cannot develop his higher mental qualities. It is said that the creation of an aristocratic element in society, whose wants are supplied by the labor and sacrifice of a less fortunate group, establishes the ideal condition for fostering the mental growth that comes from reflection and the study of the ideas of others.

There is doubtless an element of truth in each of these views regarding the conditions under which man will best develop his mental capacities. Leisure is essential to certain types of creative thought. Thought is stimulated profoundly through discussion, reading and observations of the phenomena of nature. It is not yet demonstrated, however, that such creative thought is possible or probable only in temperate regions where there are frequent and pronounced changes in temperature.

Let us now return to the relation of the diet to physical efficiency. We have, I believe, a very important problem to solve in the education

of the public in many parts of the United States in the proper selection of food. There are large numbers of people who are living too largely on diets derived almost exclusively from wheat flour, cornmeal and polished rice—all of which represent the poorest parts of the kernels from which they are manufactured—together with oats, peas and beans; tubers such as the potato, and edible roots such as the sweet potato, beet and turnip, supplemented with muscle cuts of meat. This type of diet is not satisfactory for the nutrition of an omniverous animal unless it is supplemented with milk or the leafy vegetables in liberal amounts. Of somewhat lesser value as corrective foods are eggs and the glandular organs of animals. These are, however, very low in calcium and so fail to make good this important fault in the diet.

Early aging and low vitality with consequent susceptibility to disease attend the adherence to an unsatisfactory diet. This conclusion has been forced on my co-workers and myself as the result of thousands of observations on animals restricted to diets varying in quality and restricted as to source. Variety, palatability and appropriate chemical composition as revealed by the best methods of analysis at our disposal, do not necessarily guarantee safety. Chart 3 illustrates this fact.

The general public becomes suspicious when approached by a multiplicity of councilors seeking favorable consideration when the character of their advice is so bewildering. The trouble lies in the lack of definite and accurate knowledge concerning the chemistry of nutrition that has prevailed until very recent times. While many of the wisest philosophers would agree with the statement expressed editorially by the *British Medical Journal* in 1904, "The study of dietetics should be looked upon as very nearly if not quite as important as the study of therapeutics," much disagreement would, nevertheless, be encountered in their views as to the best dietary habits to adopt. Fortunately, chemistry has come to rescue dietetics from its state of empiricism. In the hands of the chemist new methods of experimentation have been developed that have made possible the solution of problems of detail not dreamed of in the philosophy of dieticians.

There is still some scepticism among thoughtful people as to the importance of diet in its relation to health and disease. This is the natural result of several factors. In the first place we accept as normal such conditions of nutrition as we are accustomed to, until it is demonstrated that a higher standard is easily attainable. We are accustomed

Explanation of Plate III

Chart 3.—It has been customary among some investigators in recent years to assume that a diet which is capable of inducing growth at a good rate for several weeks or months is to be regarded as satisfactory. My colleagues and I have, however, reached the conclusion that judgment can be safely formed only after the effects of the diet on the life history of the animal have been observed. This, there is every reason to believe, applies also to man.

This principle is illustrated by the curves of rats fed on different diets presented in chart 3. Lot 2,152 was fed cereal products, peas, beans, calcium carbonate, and sodium chlorid. One of the animals in the group grew fairly well for three months, then failed rapidly and died.

Lot 2,153 took the same diet supplemented with 10% of round steak, which we know improved the diet essentially only in respect to the quality and quantity of its proteins. This improvement caused an acceleration in the rate of growth and made possible a period of several months of apparent well-being after growth ceased. The full adult size was not attained, however, and the fraction of its life following the completion of growth and preceding decline was very short as compared with what it is possible to attain in well-nourished animals.

Lot 2,070 was fed the same diet as lot 2,153 but further improved by the inclusion of both whole milk and cabbage. When these additions were made growth was more rapid and extended over a longer period. The span of life was greatly prolonged, the most prominent feature being the extension of the period of full vigor in adult life.

From such facts as I have been able to collect concerning the nutrition of certain of the people of India, the Bahama Islands, the Philippines and a few other places, I am led to conclude that man in some parts of the world is attempting to live on diets of about the same quality as that described in connection with lot 2,153. It would be very instructive if our geographers would seek to eliminate diet as a possible factor which complicates their deductions concerning the importance of climate in determining the achievements of man.

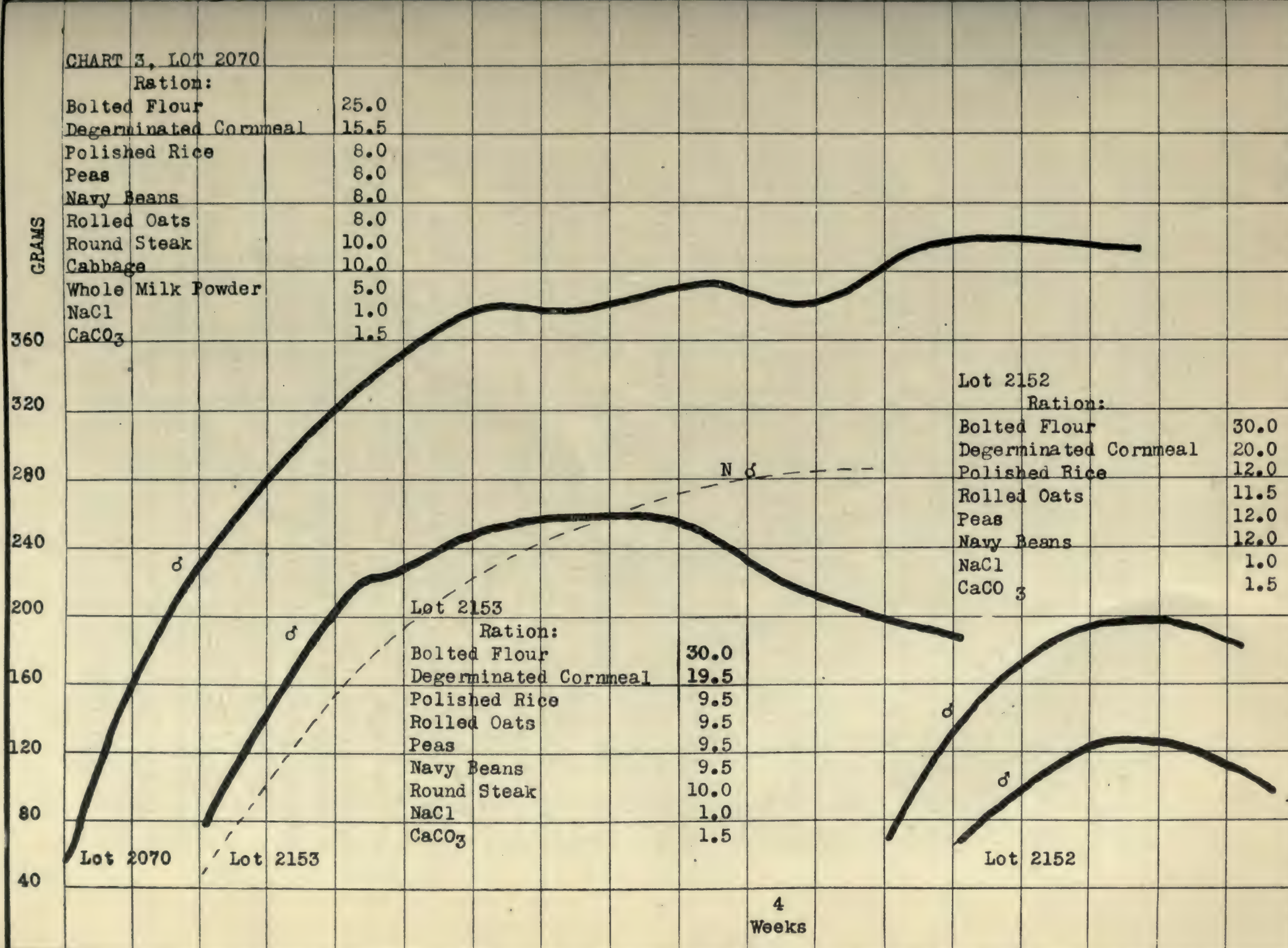


CHART 3, LOT 2070
Ration:
Bolted Flour 25.0
Degerminated Cornmeal 15.5
Polished Rice 8.0
Peas 8.0
Navy Beans 8.0
Rolled Oats 8.0
Round Steak 10.0
Cabbage 10.0
Whole Milk Powder 5.0
NaCl 1.0
$CaCO_3$ 1.5
GRAMS
360
320
280
240
200
160
120
80
40
♂
N ♂
Lot 2152
Ration:
Bolted Flour 30.0
Degerminated Cornmeal 20.0
Polished Rice 12.0
Rolled Oats 11.5
Peas 12.0
Navy Beans 12.0
NaCl 1.0
$CaCO_3$ 1.5
Lot 2153
Ration:
Bolted Flour 30.0
Degerminated Cornmeal 19.5
Polished Rice 9.5
Rolled Oats 9.5
Peas 9.5
Navy Beans 9.5
Round Steak 10.0
NaCl 1.0
$CaCO_3$ 1.5
Lot 2070
Lot 2153
Lot 2152
4
Weeks

to see people old looking at 30 to 40 years of age, and do not become impressed by it, even though the occasional preservation of vigor to an advanced age shows us what is possible.

The results of malnutrition are not such as to force themselves on the attention. It is attended by languor but not by pain. The effects of heredity and disease are not infrequently responsible for poor physical development which is scarcely distinguishable from that due to faulty nutrition. Man in different regions lives on diets that are widely different in character, and succeeds sufficiently well to seem to warrant the conclusion that it makes little difference what kind of food he takes, so long as it is wholesome and he has enough. The fallacy of such an assumption becomes apparent in the light of what we now know of the dietary properties of each of the more important natural foodstuffs. We can readily see now that man in different parts of the world is living on all the types of diet on which it has been found possible to nourish animals, and on no other. In certain places he is attempting to live on diets that cost him his vitality by the time he has reached the age which should find him enjoying the full vigor of middle life. This is the seed, tuber and meat type of diet which has already been described.

Throughout parts of India, China, Japan, the Philippines, eastern South America, Newfoundland and Labrador, beri-beri is common, and is due to faulty diet of a character which we well understand. Those who live almost exclusively on a diet of degerminated seed products, tubers, roots and muscle meats do not miss by a very wide margin developing this disease.

While scurvy has become a relatively rare disease among adults, it is still common among infants whose sole food is heated milk. We now know that the antiscorbutic substance, water-soluble C, is the most unstable complex in the diet, and is readily destroyed by heating to the boiling point of water. Many people who live almost exclusively on cooked foods come very near the point of specific starvation for this particular substance, and narrowly escape developing the disease.

Dr. Goldberger of the Public Health Service has done notable work in the study of the relation of the diet to pellagra in the South. He has pointed out that the diet of the pellagrin consists essentially of degerminated cereal grains, starch, sugar, molasses, sweet potatoes and fat pork; a very small amount of green leafy vegetables are eaten and practically no milk. He has improved the diets of the inmates of institutions where pellagra was a scourge, and observed that this leads to the

eradication of the disease. While living on a satisfactory diet, he and his associates were not able to contract the disease by material from the lesions from pellagrins and with their excreta. Further special studies, made in villages where pellagra was common, showed that families using liberal amounts of milk rarely contracted the disease, and that its incidence was highest in those households in which least milk and green vegetables were used. The liberal use of the articles that, as the result of animal experimentation, have been discovered to be corrective in character prevents the occurrence of pellagra. The question as to whether it is a disease due to an infectious agent has not been definitely decided.

It is significant that the incidence of tuberculosis among the general population of a city such as Baltimore is much higher among the group of people who live almost exclusively on the bread, meat and potato type of diet, and use least milk and green vegetables. If we may safely draw deductions from animal experimentation, it appears probable that this diet predisposes to infection with the tubercle organism.

Many will not agree with this conclusion, but hold that poor hygienic conditions and opportunity for infection, racial susceptibility and certain trades, are the factors that make this disease common. To this view I would reply that we know that the diabetic patient, whose vitality is lowered both by failure of one of the normal processes of metabolism —the oxidation of sugar—and by faulty diet, as is practically always the case, is extremely susceptible to tuberculosis. The medical profession has for many years recognized that one of the most valuable therapeutic agents in this disease is good nutrition. It is interesting to note that on purely empiric grounds the profession long ago came to the employment of a diet for the tuberculous which contained liberal amounts of milk and eggs.

Of special interest in connection with the problem of susceptibility to tuberculosis is the noncitizen Indian of today. No group of people anywhere is dying more rapidly from tuberculosis. The Indians live outdoors all summer, and probably have throughout the year as much fresh air as the average city dweller. They have abundant opportunity for becoming infected because of their careless association with infected persons, and reckless dissemination of infected sputum. Racial susceptibility has been generally regarded as a satisfactory explanation of the prevalence of tuberculosis among these Indians. It seems to me that there is another and more important factor involved, namely, the

unsatisfactory character of their food supply. The noncitizen Indian lives on a reservation and is supported by the government. He has, in general, no interest in agriculture, and does not raise much of his food. His live stock usually consists of horses. He lives on the products that he buys at the agency stores, and these, unfortunately, consist almost wholly of degerminated cereal products, legume seeds, tubers and meats. It seems plausible that this diet is an important factor in rendering him susceptible to this rather mildly virulent infection.

In the light of modern nutrition studies we have come to regard as unsatisfactory some of the diets widely used by man. We have demonstrated that, in certain respects, there is a close parallelism between the history of a poorly nourished animal and a poorly nourished man. Much remains to be learned of the finer details of the dietary habits of man in various parts of the world, and of the health conditions with which these can possibly be correlated. It has seemed, however, that we have succeeded in correlating certain data relating to human nutrition with the results of laboratory studies in a manner which brings to light a most important principle in the selection of foods. If these deductions are sound, it is evident that one of the great tasks of the general undertaking of raising the standard of public health is the education of the public along two lines: the extension of the use of dairy products, and the cultivation of the habit of eating more freely of green leafy vegetables than is now the practice in the United States.

BIBLIOGRAPHY

Chick, H., and Hume, E. M.: Tr. Soc. Trop. Med. and Hyg., 1917, 10, p. 141.
Chick, H., and Delf, E. M.: Biochem. Jour, 1919, 13, p. 199.
Cohen, B., and Mendel, L. B.: Jour. Biol. Chem., 1918, 35, p. 425.
Goldberger, J., Wheeler, G. A., and Sydenstricker, E.: Jour. Am. Med. Assn., 1918, 71, p. 944.
Holst, A., and Frolick, T.: Jour. Hyg., 1907, 7, p. 634.
Huntington, E.: Climate and Civilization, 1915.
Little, A. D.: Jour. Amer. Med. Assn., 1912, 58, p. 2029.
McCollum, E. V.: The Newer Knowledge of Nutrition, 1918.
McCollum, E. V., and Davis, M.: Jour. Biol. Chem., 1915, 23, p. 231.
McCollum, E. V., Simmonds, N., and Pitz, W.: Ibid., 1917, 30, p. 13.
Maupas, E.: Arch. de zool. exper., 1889, 6.
Palmer, L. S.: Science, 1919, 50, 501.
Steenbock, H.: Ibid., 352.
Woodruff, L. L.: Proc. Soc. Exper. Biol. and Med. 1912, 9, p. 121; Jour. Exp. Zool., 1914, 16.

REMARKS ON THE CHEMISTRY OF THE PROTEIN MOLECULE IN RELATION TO INFECTION

ABSTRACT

Victor C. Vaughan

University of Michigan, Ann Arbor, Michigan

January 30, 1920

About twenty-five years ago I decided to give the greater part of my time to study of the chemistry of bacterial cells. The first thing to do was to get the cell substance in large amounts, relatively free from contamination. Up to that time, bacteria had been grown in test-tubes and Roux flasks, the latter containing the largest cultures made. I tried Roux flasks. I inoculated 100 of these flasks. The bacteria grew abundantly, but when I attempted to detach the growth and fish it out of the relatively small neck of the bottle it was so difficult that I had to give it up. Next I tried to grow bacteria in moist chambers, but found that, using every precaution, they invariably became contaminated; and finally, in 1900, I devised copper tanks for growing bacteria in massive cultures. Some of you have seen these tanks and others have seen the illustrations. By means of these tanks I was able to obtain bacterial cell substance in large amounts — literally by the pound, of pure cell substance. It cost at that time $75 to load my nest of six tanks, each tank being 10 feet long and 2 feet wide, so that with the six I grew 120 square feet of germ substance at a time. I imitated the scientific farmer and rotated my crops. As a routine, I inoculated my tanks with pneumococcus and grew this organism at from 38 to 40 C. for 4 days; then I removed the growth, resterilized my medium, and planted typhoid bacilli. I found that typhoid bacilli grew just as well after pneumococci as on perfectly fresh material. After the growth of typhoid bacilli had been removed, I resterilized and planted the colon bacillus. Usually I got two good crops of this organism. After removing the second crop of colon bacilli I grew other crops of non-pathogenic bacteria. A good yield from the 6 tanks often gave me as much as 500 gm. of pure bacterial cell substance. The growths were detached with sterilized bent glass rods and pulled into sterilized receptables by means of a water pump. The bacterial substance was washed first with salt solution and then extracted for 3 days with

absolute alcohol and for 4 days with ether. In all cases this treatment left a white powder, all the coloring matter having been removed by the extractions.

The extracted cell substance was ground first in porcelain and then in agate mortars. The only accident of any note happened while grinding the bacilli. We found it necessary to wear masks, and even when this was done and typhoid bacilli were being ground, the one who did this for the first time had within from 4-6 hours a severe chill followed by a temperature which ran as high as 106 F. After the subsidence of this fever there was no further trouble. I found that this cellular substance under the microscope showed the bacilli as normally as they appear in fresh specimens. The pneumococcus, for instance, appeared quite as normal after this treatment as it does in a specimen of sputum. I found that this dead cellular substance, injected into animals, did them harm, and I found — strange to say — that it harmed in inverse proportion to the infectivity of the living organism. Note that the prodigiosus, a nonpathogenic organism, killed guinea-pigs when injected into the abdominal cavity, one part to two or three million parts of body weight, while the anthrax bacillus required one part of cellular substance to 1,400 parts of body weight. In no amount did the tubercle bacillus kill fresh animals. The more infectious an organism is, so far as those with which I worked are concerned, the less toxic I found it when injected into animals. Understand that I am saying nothing about toxins or antitoxins or toxin immunity. I am talking about micro-organisms that produce no extracellular toxins. The word "toxin" has come to have a definite meaning. It is a substance which, when injected in repeated nonfatal doses, causes animals to produce an antitoxin. I do not refer to diphtheria or tetanus, or any of the bacteria which produce soluble toxins. So far as the endotoxin of Pfeiffer is concerned, I have never found such a thing. In other words, I have never found in any cell substance a substance which, when injected into animals, produces an antitoxin. The protein poison is not a toxin. I found that the dead substance, injected into animals, produces the same lesions that follow inoculation with the living bacillus. When I inoculated an animal with the typhoid bacillus or the colon bacillus intra-abdominally I got the same symptoms and the same lesions as when I injected living typhoid or colon bacilli. I concluded that it is not the growth and multiplication of bacteria in the animal body that causes the symptoms and lesions of the disease.

When I was a student I was taught that the characteristic lesions which we find in the intestine in typhoid fever result from the gnawing action of typhoid bacilli in their attempts to get through the intestinal wall into the blood. Indeed, for some years I taught the same thing. Today we admit that this is not the case, and that typhoid bacilli in passing from the alimentary canal into the blood produce no recognizable lesions and that the lesions which we find in the majority of cases — not in all — after death from typhoid fever are due to the elimination of poisonous substances from the blood and do not indicate the port of entry of the bacteria. I wish to say, parenthetically, that many years ago I tried to induce ulceration in the stomach and intestine by feeding animals with arsenic. I did not succeed, but I found that it was relatively easy to induce these ulcerations by giving a preparation of arsenic hypodermically or intravenously. Moreover, on looking up the literature I found that this method of producing gastric and intestinal ulceration was known one hundred and fifty years before I made my experiments.

As I have said, the effects after the administration of dead bacterial cell substance are the same or at least very similar to those which follow inoculation with the living organism, and that the effects of the dead substance are inversely proportional to the infectivity of the living organism. Why is it that the prodigiosus is nonpathogenic to guinea-pigs? I should say it is because the normal secretions of the body cells destroy these bacilli as soon as they get into the blood. In other words, the body cells are already sensitized to this organism. Therefore it follows that if you take enough of the dead cellular substance of the prodigiosus and inject it into the abdominal cavity of a guinea-pig, immediately the normal fluids of the body split up the cells of the prodigiosus, and if the quantity be sufficient it kills the animal. In my opinion the infectivity of a bacillus or other virus depends on two conditions:

1. Will it grow in the animal body? If it will not grow in the animal body it cannot cause infection. A given organism must grow and multiply in the body in order to be infectious, and in doing so it must be able to feed on the substances of the body. If it is not able to do this, it cannot be infectious to that animal.

2. Whether a given organism is pathogenic to a given animal or not will depend on whether the fluids of the body kill that organism as

soon as it is introduced into the body. If this does not happen, and if these two conditions are favorable, the micro-organism grows and multiplies in the body and causes infection.

I attempt to explain vaccination in this way. The smallpox virus is pathogenic to the person who has not had smallpox, or to the man who has not been vaccinated. To the person who has had smallpox or who has been successfully vaccinated the smallpox virus is not pathogenic. When you vaccinate a child against smallpox you introduce into the body a modified smallpox virus. It grows slowly and the body cells are educated and trained to destroy this virus. When subsequently the child is exposed to smallpox the first smallpox virus that gets into the body is split up and destroyed, and there is no growth and no disease.

We vaccinate against typhoid fever by taking the dead bacillus and injecting it into the individual three or four times at intervals. In so doing we are training the body cells to digest the typhoid protein and subsequently when the man drinks water that contains typhoid bacilli, as soon as the first organisms get into the body they are split up and destroyed, and the man escapes typhoid fever.

Twenty years ago I made the statement that typhoid and like vaccinations will not give absolute protection. Such protection is always relative and may be overcome by massive inoculations. From experience in the late war we know that massive doses of typhoid bacilli may cause typhoid fever in the vaccinated. Furthermore, we have learned that typhoid fever in the vaccinated differs neither in symptomatology nor in lesions from that in the unvaccinated. An unwarranted faith in the value of vaccination against typhoid fever gave some of our medical officers in France a feeling that this disease could not occur among our troops. It happened, therefore, that in at least one instance typhoid fever was first recognized at necropsy.

If we inject into the abdominal cavity of a guinea-pig a virulent culture of the colon bacillus and then observe the symptoms, we shall find them to be about as follows:

For some hours there is no recognizable difference between the inoculated animal and his fellows. Their behavior is the same. Then, rather suddenly, something goes wrong with the inoculated animal. It begins to shiver, its coat gets rough; it huddles up among its fellows; it goes off its food; something is wrong. For a while its temperature may be above the normal, but in a short time it begins to fall and con-

tinues to do so until the animal dies. At necropsy one finds an exudative hemorrhagic peritonitis. If something like the minimum fatal dose has been administered, it will be about twelve hours before the animal shows any changes. This is the period of incubation, and it occurs in every infectious disease. During this time, the bacilli rapidly multiply in the body. They are feeding on body substances. They are converting guinea-pig substance into typhoid substance, and the process is a synthetic one. They are taking relatively simple bodies, probably only amino acids, and building them into typhoid protein. During the period of incubation of an infectious disease the invading organism furnishes the ferments and the body of the host supplies the substrate or food, and the processes are synthetical. Simple bodies are built into more complex ones. There is no poison set free, there are no lesions, and there are no symptoms. Therefore it is not directly the growth and multiplication of bacteria in the body that cause the symptoms and lesions of the infectious diseases.

Really the period of incubation is a critical time, as it always to some extent at least determines how rapidly the bacteria grow. The invading organisms multiply in the body until the body cells become sensitized and pour out a secretion that splits up and destroys the invading organisms. During the active stage of an infectious disease the body cells supply the ferment, the invading organisms furnish the substrate or food; the processes are analytic; complex bodies are split into simple ones; a poison is set free, and the symptoms and lesions of the disease develop. I do not desire to give the impression that I believe there is a sharp line between the processes of incubation and those of the active disease. The two may be going on side by side in adjacent tissue. The sensitization may be local or general. In the former instance, a local disease develops; in the latter, the disease is systemic. The sensitization may come on suddenly and with virulence; it is then an acute disease. It may come on slowly and gradually extend, and it is then a chronic disease. It is the destruction of the bacilli in the body that causes the symptoms and lesions of the disease.

To a second guinea-pig we give in place of a living culture the dead cellular substance of the colon bacillus. This organism has been grown in vitro. There is no chance for multiplication in the body. The period of incubation is now shortened. Dead cellular substance, having no resistance, sensitizes the body cells more quickly than living bacilli. After sensitization occurs we have exactly the same symptoms that

we had in the animal that we had inoculated with the living culture. On postmortem examination we find the same exudative hemorrhagic peritonitis.

My assistants and I worked for some years in our endeavors to find methods for splitting bacterial cell substance into poisonous and nonpoisonous parts. The method which we finally adopted was to boil the cellular substance at 78 C. in absolute alcohol in which 2% of sodium hydroxid had been dissolved. An aqueous solution of the same alkali will produce the same result, but in this case both the poisonous and nonpoisonous parts will be in solution. When absolute alcohol is used the poisonous part is soluble in the alcohol, while the nonpoisonous part is not.

Having found that pathogenic bacterial cell substance could be split into poisonous and nonpoisonous portions it was quite natural that we should attempt to find out whether nonpathogenic bacterial cell substance could be split in the same way. I have already indicated that we found this to be true. Next we tried animal and finally vegetable proteins. To be brief, we came to the conclusion that all protein molecules contain a poisonous portion. As I have indicated, this is a poison, and not a toxin. In its gross effects on animals this poison is the same, whatever the protein from which it has been derived. I dare say that it will be found on closer study that there are differences in chemical composition and structure, between the protein poisons obtained from widely different proteins. It is interesting to remark that so simple a protein as casein will furnish enough protein poison to kill guinea-pigs when it is injected intravenously. I am sorry that I have not shown myself to be a sufficiently skilled chemist to work out the chemical structure of the protein poison. I must leave this for more competent men. The dose of the poison necessary to kill a guinea-pig when injected intravenously is about 0.5 mg.

We have made many attempts to induce immunity in animals with the protein poison. We have found, and others have confirmed this, that a certain degree of tolerance may be established by repeated doses of this substance. This tolerance is not marked. I do not think that it should be called a form of immunity. Still I am inclined to believe that it has an important part, under certain conditions, in securing immunity. If guinea-pigs or rabbits that have been treated with successive doses of the protein poison, and so trained that they will stand without harm two or three times the ordinary fatal dose, be inoculated

with a living organism, it requires more of the culture to kill these animals than it does to kill fresh animals. In other words, increased tolerance to the protein poison enables an animal to bear at least one fatal dose of the living organism. When it recovers from the living organism it has acquired a specific immunity. In this way I have attempted to explain the often observed and frequently recorded fact that the seasoned soldier withstands epidemics to which the raw soldier succumbs.

In our observations on the fatality of the acute respiratory diseases in our armies during the war two facts stood out prominently. It was at first observed that the soldiers from rural districts succumbed in larger numbers to these diseases than those from densely crowded cities. The other fact equally striking was that when an epidemic struck a camp the recently recruited men died in larger numbers than those who had been in the camp for months. In the fall of 1917-18 it was observed that men recruited from rural communities showed a much higher death rate from the respiratory diseases than those from densely populated cities. When influenza struck the camps in the fall of 1918 recently recruited men died in larger numbers than did those who had been in camp for months. I have attempted to explain these observations on the ground that men from large cities and men who had been in camps for many months have acquired an increased tolerance to the protein poison. When measles or influenza came they were not immune to these new infections, but they bore them better, and in doing so, acquired a specific immunity. In one camp one-tenth of the command had been in camp less than one month when influenza appeared. This one-tenth furnished 30% of the deaths. Similar observations have been made in all wars, and in other armies during this war.

THE RELATIONS OF PROTEINOGENOUS AMINES TO MEDICINE

KARL K. KOESSLER

January 30, 1920

INTRODUCTION

The injurious action which pathogenic micro-organisms exert on the human organism is almost entirely effected by chemical means. Yet our comprehension of the chemical processes by which bacteria produce disease and our knowledge of the chemical constitution of the poisonous substances evolved by their metabolism is in a very elementary state. To the student who would venture to dedicate his life-work to the investigation of the chemical factors in the pathogenesis of infectious diseases, the history of the last thirty years of the Nineteenth Century tells a tale that merits his reflection.

About the time when Pasteur, in France, had communicated his fundamental researches on fermentation and putrefaction, proving that these two processes depended invariably on the presence and activity of living micro-organisms, another chemist, in Italy, Selmi, was occupied in investigating the end-products of putrefaction found in human bodies after death. Selmi observed that basic compounds occcurred in the animal organism of similar chemical character as the alkaloids of vegetable origin, giving reactions like those of coniin, nicotin, atropin, delphinin and strychnin. Since he found these putrefactive alkaloids chiefly at the medicolegal examination of corpses, he gave them the name ptomaines, from πτῶμα — corpse. Selmi worked entirely with the extracts of the putrefied material and recognized the proper solvents in ether, chloroform and amylalcohol, but he himself never succeeded in isolating a single ptomaine in pure crystalline form. This achievement was accomplished by Nencki, one of the most eminent investigators in the field of chemical bacteriology. Nencki, in 1876, first isolated and analyzed correctly a base of the formula $C_8H_{11}N$ obtained in the putrefaction of gelatin and identified it later as phenylethylamin. Of the large number of investigators that followed Selmi and advanced this field, Gautier, in France, and Brieger, in Germany, were the most successful. By using new precipitating agents like the chlorids of the heavy metals, as mercuric and platinic chlorid, they

isolated many ptomaines of definite chemical composition and investigated their chemical, as well as their physiologic, properties. From organs, meat and foodstuffs, which had undergone putrefactive changes, Brieger isolated mono-amines (mono, di- and, trimethylamine, ethyl, amyl, and butylamine), diamines (putrescin and cadaverin) as well as cholin, muscarine and methylguanidine. In addition to these, he isolated a large number of compounds, so complicated that only their elementary composition could be determined. It became more and more apparent, especially under the influence of the work of Nencki and his school, that all these basic substances were formed as the result of the action of bacteria, on protein and phosphatids. By the early 80's it had been definitely proved that micro-organisms could cause disease, and adherents as well as opponents of the germ theory, constantly raised the question: How do germs produce disease? Brieger, with his followers, applied his methods to the culture mediums in which the bacteria grew, and succeeded in isolating from these a variety of ptomaines. Brieger himself isolated four different ptomaines from the culture filtrate of the tetanus bacillus, and later on, a typhotoxin from the typhoid bacillus, Rosenbach and Nicolaier described a tetanin, and in this way it was believed by many that bacteria caused infectious disease by virtue of these products of decomposition of the material on which they grew. This was soon proved to be a fallacy, for it was impossible with ptomaines alone to produce the characteristic symptoms of disease or the distinctive pathologic changes, whereas both could readily be produced by the injection of the culture fluid containing the bacteria. Ptomains produced by virulent organisms proved to be slightly toxic, whereas some nonpathogenic bacteria would form extremely poisonous substances. The ptomaines were found not to be specific for any one special micro-organism, nor could antibodies be produced in response to their injection into animals.

Not the study of the ptomaines, but researches on the true toxins and endotoxins, those soluble and intracellular poisons manufactured by the bacterial cell, brought about the new era in medical therapy. Antitoxin immunity and vaccination with attenuated cultures and virus accomplished results that heretofore were unknown in the history of medicine. It mattered little that the chemistry of these toxins and antitoxins was, and remained, unknown. Never before were short cuts in science more justified by the results. By new methods, not

chemical, Pasteur, the chemist, had opened this new continent, and with him Koch, Roux, Behring, Kitasato and Ehrlich plowed the fields on the fruits of which all medical men of today are living.

Thus it came about that just those bacterial poisons that chemically were the best characterized and studied, the ptomaines, were proved to be of little value in explaining the phenomena of infection and immunity, and in fighting disease. Although it is admitted that certain cases of food poisoning may be brought about by the action of ptomaines formed from the food by bacterial decomposition, most of these instances are proved to be the result of bacterial infection with the bacillus enteritidis or paratyphosus, or of bacterial toxin action, as in the case of the bacillus botulinus. The educated physician of today shrinks from using the word ptomaine, too often a misnomer for diagnostic ignorance and always tainted with the bad odor of its history.

This premature application to human pathology of the new facts gained from the study of the chemical substances formed during putrefaction proved to be an error, but the facts were correct and the knowledge of the process of putrefaction had been materially advanced. From this time the study of the putrefactive bases as being the result of the action of bacteria on protein and phosphatids, became more and more closely allied with the chemistry of proteins and of their building stones, the amino acids.

RELATION OF THE AMINES TO PROTEIN

When protein is disintegrated in the intestinal tract by the digestive activity of trypsin and erepsin, the result is the liberation of substances of simple structure, which are known as amino acids. These units are likewise obtained if the cleavage of the protein is brought about in the absence of the secretory enzymes of the digestive organs by the fermentative activity of micro-organisms, and this bacterial decomposition of protein matter to amino acids represents the first stage in the process of putrefaction. There are known at present some twenty different amino acids; they are absorbed — in part at least — intact from the intestinal lumen into the circulation and serve as food in the rebuilding of the tissue of every organ. All of them seem to be physiologically inert and, if introduced directly into the circulation, have no immediate pharmacodynamic action.

The decomposition of protein by bacteria or by organ cells does not stop when the amino acid stage has been reached. Bacteria have the

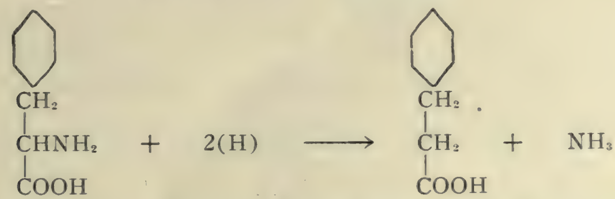
faculty of breaking the amino acids into smaller pieces, and some of these fragments are extremely toxic. There are two main routes over which this katabolism of amino acids may proceed.

First: The amino group is detached, ammonia is split off and the next lower fatty acid is formed from the amino acid over the keto acid and aldehyd. This process is commonly accomplished by oxydation and is known as oxidative deamination. Thus alanine may be converted into acetic acid:

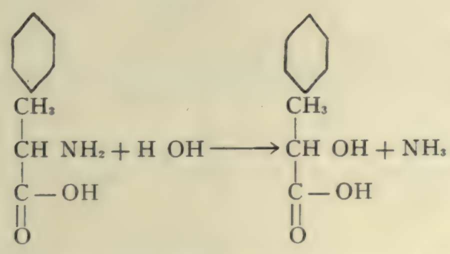
$$\begin{array}{l}CH_3\\ |\\ CHNH_2\\ |\\ COOH\end{array} + (O) \longrightarrow NH_3 + \begin{array}{l}CH_3\\ |\\ C=O\\ |\\ COOH\end{array} \longrightarrow \begin{array}{l}CH_3\\ |\\ C=O\\ H\end{array} + CO_2$$

$$\begin{array}{l}CH_3\\ |\\ HCOH\\ H\end{array} \longleftarrow \text{(reduction) } 2\,(H) + \begin{array}{l}CH_3\\ |\\ C=O\\ H\end{array} + (O) \text{ (oxidation)} \longrightarrow \begin{array}{l}CH_3\\ |\\ COOH\end{array}$$

Anaerobic bacteria frequently reduce amino acids; ammonia is liberated and a saturated fatty acid formed. Thus phenylpropionic acid is formed from phenylalanine by this reductive deamination.



In rarer instances the oxyacid is formed from the amino acid by hydrolytic deamination.



By the activity of yeasts, on the other hand, alcohols are formed from the amino acids by hydrolytic deamination.

$$CH_3\ CH\ NH_2\ COOH + H_2O \longrightarrow CH_3\ CH_2OH + NH_3 + CO_2$$

Deamination is often followed by decomposition of the carboxylic acid formed, and by oxidation and demethylation. By this series of reactions paracresol and phenol are formed from tyrosin, skatol and indol from tryptophan. These are the compounds we are in the habit of thinking of when we hear the word putrefaction.

The second main route by which the breakdown of amino acids may proceed is the one to which I particularly wish to direct your attention. The carboxyl group is removed from the amino acid group by the splitting off of carbon dioxid. This process is known as decarboxylation. It may happen before or after deamination. If it precedes the splitting off of NH_3, basic substances, amines, of remarkable physiologic properties, are formed, and we define accordingly as proteinogenous those amins that are derived from amino acids by decarboxylation.

In this manner:

$$CH_2NH_2—COOH \rightarrow CH_3NH_2 + CO_2$$

$$CH_3—CHNH_2—COOH \rightarrow CH_3—CH_2NH_2 + CO_2$$

$$(CH_3)_2CH—CHNH_2—COOH \rightarrow (CH_3)_2CH—CH_2NH_2 + CO_2$$

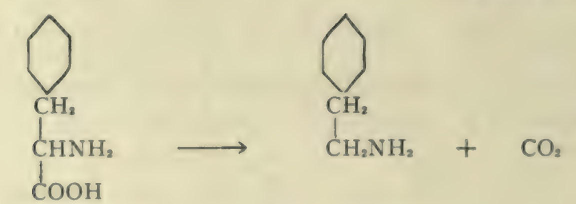
$$(CH_3)_2CH—CH_2—CHNH_2—COOH \rightarrow (CH_3)_2CH—CH_2—CH_2NH_2 + CO_2$$

$$H_2NCH_2—CH_2—CH_2—CHNH_2—COOH \rightarrow H_2NCH_2—CH_2—CH_2—CH_2NH_2 + CO_2$$

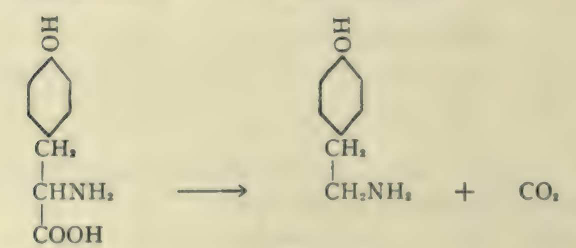
Ornithine Putrescine

$$H_2NCH_2—(CH_2)_3CHNH_2—COOH \rightarrow H_2NCH_2—(CH_2)_3CH_2NH_2 + CO_2$$

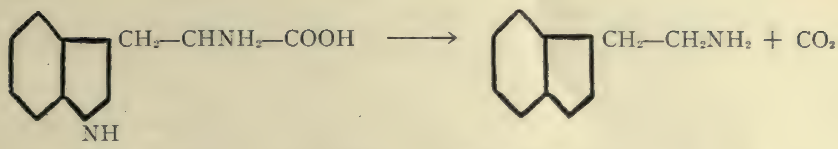
Lysine Cadaverine



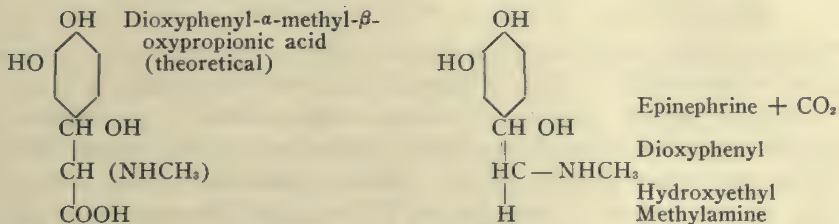
Phenylalanine Phenylethylamine

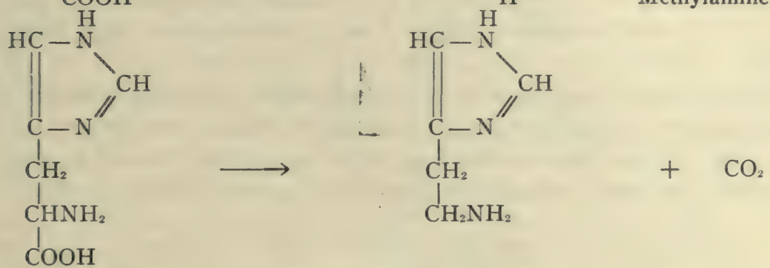


Tyrosine Tyramine



Tryptophane Indolethylamine





Histidine Histamine

The removal of the CO_2 might be accomplished in various ways.
1. Directly

$$NH_2CH_2 - + \underset{\substack{+ \\ \overline{OH}}}{C\ddagger} = O \longrightarrow NH_2CH_3 + CO_2$$

2. By dissociation into the methylene derivative and formic acid and subsequent reduction of the first to the amine.

$$H_2N - \underset{\substack{| \\ H}}{\overset{\substack{H \\ |}}{C}} - COOH \longrightarrow CH_2 = NH + HCOOH$$

$$HCOOH \longrightarrow CO_2 + 2(H)$$

$$CH_2 = NH + 2(H) \longrightarrow CH_3 - NH_2$$

and

3. By hydrolysis.

$$H_2NCH_2\text{—}COOH + H\text{—}OH \longrightarrow H_2NCH_3 + HO\text{—}COOH$$
$$\downarrow$$
$$CO_2 + H_2O$$

which is similar to the hydrolysis of trichloracetic acid

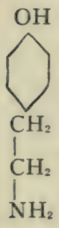
$$Cl_3C\text{—}COOH + H\text{—}OH \longrightarrow Cl_3CH + HO\text{—}COOH$$

This seemingly simple chemical process, the decarboxylation of amino acids to exceedingly potent substances of amine structure is of great theoretical, as well as practical, interest. The relation of this problem to the general nutrition of bacteria, to the metabolism of amino acids in the mammalian organism, to the pathology and pharmacology of the smooth muscle fiber system and to the chemical constitution of the glands of internal secretion, stamps it as a fundamental inquiry of biology.

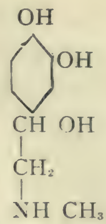
The systematic investigation of certain phases of these problems has been under way in the Sprague Institute for Medical Research for several years. But, before referring to our own work, I wish to discuss briefly the truly remarkable physiologic action of these amines.

PHYSIOLOGIC AND PHARMACODYNAMIC ACTION

From the point of view of chemical composition they might be divided into two classes: the mono amines, like isobutylamine, isoamylamin phenylethylamine, p. hydroxyphenylethylamine and indolethylamine, which have one basic N group; and the diamines, as tetramethylene diamine and pentamethylene diamin (putrescin and cadaverin) agmatine, the amine derived from arginine, and imidazolethylamine, which have two basic N groups. This difference in the chemical composition of each group is associated with a corresponding diversity of physiologic action. The most active compounds are those that have a ring structure with a side chain of two carbon atoms. As representative of the monoamines, p. hydroxyphenylethylamine will serve for our discussion. P. hydroxyphenylethylamine is derived from tyrosine by loss of carbon dioxide and is therefore also called tyramine. When injected intravenously in quantities of 1-2 milligrams into cats, dogs and rabbits it causes a sudden marked rise in blood pressure. This rise in blood pressure is pronounced and inferior only to the one produced by epinephrine, to which tyramine bears a striking similarity both pharmacologically and structurally.



Tyramine



Epinephrine

While the rise in blood pressure of p. hydroxyphenylethylamine is lower and slower than that of epinephrine, its duration is somewhat longer. Dale showed that the rise of the arterial pressure is partly due to an increased output of the heart, chiefly, however, to a vaso constrictor effect on the arterioles, peripheral in origin. In its action on the uterus, tyramine too resembles adrenaline; it inhibits the activity of the nonpregnant uterus causing relaxation of tonus in the cat, but produces intense contractions of the pregnant uterus. Thus the action on the animal organism produces symptoms which are similar to those produced by stimulation of the sympathetic nervous system. Especially marked is this action on the involuntary musculature of the eye. The intravenous injection of p. hydroxyphenylethlamine in the cat produces dilatation of the pupil, retraction of the nictitating membrane, widening of the palpebral fissure (lagophthalmus), protrusion of the eyeball (exophthalmos), and secretion of tears. Even after extirpation of the superior cervical ganglion these effects are still produced and they must therefore be considered peripheral in origin like similar effects of adrenaline. Of effects on gland cells, beside the lacrimal secretion, we might mention further the action on the sweat glands and submaxillary glands, sweat and saliva being secreted profusely. The flow of urine from the ureters is distinctly increased, but the pancreatic secretion is not visibly influenced and no glycosuria is produced even if as much as 100 mg. are given hypodermically. Nor does parahydroxyphenylethylamine show the dilatating effect on the smooth muscle fiber system of the bronchi, so characteristic of the action of epinephrine. Another important difference in the action of the two bases is shown in their mode of absorption by the organism. The action of epinephrine is almost entirely lost if given by mouth, while the tyramine retains its activity by this channel of absorption, producing all the symptoms of stimulation of the sympathetic nervous system in a marked degree.

The action of p. hydroxyphenylethylamine on the circulation in man is comparable to that in animals. If injected subcutaneously in doses from 0.02 to 0.06, it causes considerable elevation of blood pressure lasting for several hours. The increased systolic pressure is associated with a heightened pulse pressure and an increase of the volume pulse in the arm; the heart rate is retarded. In the electrocardiogram the ventricular complex shows an increase in the size of the T wave and the occasional occurrence of extra systoles (Hewlett).

The physiologic activity of parahydroxphenylethylamine was first revealed by Barger and Walpole, who recognized it as the chief pressure principle in extracts of putrid meat along with isoamylamine and phenylethylamine, which have a similar though lesser action.* On inoculating a culture medium of tyrosin with a small amount of human feces, Barger and Walpole were able to extract a substance which in the animal experiment behaved like parahydroxyphenylethylamine. This result induced them to express the probability that the amines isolated from putrid meat (parahydroxyphenylethylamine, phenylethylamine, and isoamylamine) are normally formed by putrefaction in the human intestine. Preceding this work of Barger and Walpole on the pressure principles of putrid meat, Dixon and Taylor had made the interesting observation that alcoholic extracts of the human placenta contained substances which on intravenous injection produced a rise of blood pressure and contraction of the pregnant uterus. But it was soon shown by Rosenheim that this effect was given only when the placentae had undergone putrefactive changes, as evidenced by the presence of micro-organisms. Dixon and Taylor had used an amount of alcohol, which, when mixed with the water content of the placenta, was insufficient to prevent putrefactive processes. When perfectly fresh placentae with sufficient absolute alcohol were used, no blood pressure raising substances could be extracted. The active substances were later identified as parahydroxyphenylethylamine and isoamylamine.

When parahydroxyphenylethylamine is given either by intravenous injection or by mouth for a long period of time, the effects of this slow, chronic poisoning are remarkable. Harvey fed and injected rabbits with gradually increasing doses of a 2 per cent. solution of tyramine,

* The discovery that extracts of putrefied meat raise arterial blood pressure on intravenous injection is usually ascribed to Abelous, who reported on this subject in 1906. But 50 years earlier P. L. Panum had discovered and described this fact showing that the poisonous substance retained its activity after boiling for 11 hours and after treatment with absolute alcohol.

over a period varying from 80 to 300 days. At the postmortem examination he found that 20 out of 33 animals showed renal lesions; in 25 there were lesions of the tunica media of the arteries; in 10 animals the enlarged heart showed fibrous changes. The daily subcutaneous injection of 3 mg. of parahydroxyphenylethylamine over a period of 2 weeks produces a severe anemia which leads to the death of the animal. The morphologic changes in the blood, as well as in the bone marrow, recall vividly the picture of true pernicious anemia in man (Iwao).

It might be mentioned that besides putrefied meat, other protein-containing material in a state of slow decomposition has been shown to contain the substance under discussion, such as several varieties of cheese: Cheddar and Swiss, and Japanese soja beans.

Another source of parahydroxyphenylethlamine which deserves our attention from different points of view, is ergot. Until about 10 years ago the action of this drug on uterus and blood vessels was ascribed to the presence of several alkaloids, such as ergotoxine, ergotinine, sphacelotoxin, cornutine and others. But as the result of the work of Rielander, Ackerman and Kutscher on the continent, and Barger and Dale in England, it was found that watery ergot extract contained parahydroxyphenylethylamine, isoamylamine, phenylethylamine, B imidazolethylamine, penta- and tetramethylenediamine and agmatine, and that the action of ergot on the uterus and blood vessels could be explained on the basis of the combined pharmacodynamic effect of these amines. It is still an open question whether these bases are produced entirely by the enzymes of the fungus itself, or by bacterial action during the not sterile process of extraction. In either case the notorious variability of the official liquid extract is readily intelligible.

This brings us to the second group of the simple amines derived from proteins: the diamines, which contain two nitrogen groups. To this group belong indolethylamine, the amine derived from tryptophane by loss of CO_2, putrescine and cadaverine, agmatine, the amine derived from arginine, and imidazolethylamine or histamine, the base derived from the amino acid histidine. The amine derived from tryptophane indolethylamine regarding its physiologic activity takes an intermediate position between the sympathomimetic monamines as represented by epinephrin or parahydroxyphenylethylamine and the diamines such as imidazolethylamine. The chemical structure shows a beautiful correlation to this physiologic action, for while the molecule of indolethylamine has two nitrogen atoms, only one of these is basic in nature.

We stated that the most active of these compounds are the cyclic amines with a side chain of two carbon atoms. Of the diamines it is the amine derived from histidine (α amino B imidazolepropionic acid) which shows such a structure. Its chemical name is B imidazolethylamine, but it may be appropriately called by its shorter name histamine. The physiologic behavior of this amine is primarily characterized by its stimulating effect on the smooth muscle fiber system.

If a guinea-pig weighing 300 to 500 gm. receives an intravenous injection of 0.5-1.0 mg. of histamine, the animal shows, a few seconds after the injection, a state of restlessness and exaltation. This is sometimes preceded by violent scratching of the ears, nose, and the skin of the body which can be reached by the paws of the posterior extremities. The guinea-pig, after a few turning movements, sits in a sprawling position; the heart beat is accelerated, and the respiration, first rapid, soon becomes irregular and labored. The animal passes urine and often feces. Suddenly it begins to run as though fleeing from an invisible enemy, then stops, and after several ineffective respiratory efforts, it falls to one side; the visible mucous membranes of the nose and of the genital region show a high degree of cyanosis. After a few veritable respiratory convulsions the animal dies, plainly a death from acute suffocation. At postmortem the lungs are found to be completely and permanently distended by air, they do not collapse, and are of a pale, anemic appearance, and sections show the bronchioles completely obturated as a result of a tetanic constriction of the smooth muscle fibers surrounding them. Atropine possesses a protective action against this death from acute emphysema and bronchospasm. When larger doses of histamine (3 mg.) are given to the guinea-pig intraperitoneally, a gradual fall of temperature from 38.5-28.5 degrees may be observed in the course of two hours. The animal usually recovers, and the following day the temperature is again about 38 degrees (Dale and Laidlaw). Very small doses, on the other hand, may produce a transitory rise in temperature (Pfeiffer, 1911).

In this picture is recognized the close resemblance to the syndrome produced by poisoning with so-called Witte's peptone, with Vaughan's poisonous fraction of the split protein, and to the protein intoxication following the reinjection of previously sensitized animals known as anaphylactic shock. The chief point of difference lies in the lack of coagulability of the blood brought about by the injection of peptone,

which is present only to a slight degree on the injection of histamine. Another point of similarity to anaphylactic shock is shown by the identical behavior of different species of animals to the amine as well as to the anaphylactic poison. Dogs show a much greater resistance to both forms of poisoning, the chief symptom being a gradually increasing excessive fall of the arterial blood pressure. The possible relation of histamine shock to surgical or traumatic shock is suggested by the study of the effect of this amine on the circulation in the anesthetized cat (Dale). The nonanesthetized cat tolerates large doses; it goes into collapse and coma, but recovers. If the same animal is put under an anesthetic "even moderate doses of histamine will produce a fatal circulatory collapse and respiratory failure, from which the animal does not recover even after prolonged application of artificial respiration." Analysis of this shock shows that the diminution of the output of the heart almost to the point of extinction is the principal factor of the circulatory collapse. This failing systolic output from the heart is due to inadequate filling during the diastole, the greater part of the blood collecting in the capillaries of the voluntary muscles. The fall in blood pressure is very marked, in some cases from 160 to 40 millimeters mercury; the blood viscosity, the corpuscular content and hemoglobin increase, due to loss of blood plasma and its passage into the tissues. But this "leakage of plasma from the vessels into the tissues, with the reduction in the volume and increase in the viscosity of the blood, cannot be the main cause of the shock, though it doubtless accentuates its severity. The characteristic features of the condition are not so much due to the fact that the volume of the blood is reduced, as to the tendency of what remains to stagnate in the periphery in the capillaries and venules instead of returning to the heart; this peripheral accumulation of blood is the effect of a general relaxation of the capillary vessels."

That chemical factors might be involved in the production of traumatic shock has been made probable by the work of Bayliss and Cannon, who showed that on extensive injury to the tissues of a limb, the nervous connection of which with the rest of the body has been severed, shock results; but if the blood vessels are clamped, shock is prevented. They reason that through the injury of the tissues substances are produced which on absorption into the general circulation, produce shock.

The action of histamine on the organs of the smooth muscle fiber system is best illustrated by its faculty to contract the smooth muscle fibers of the nonpregnant uterus in as small a concentration as 1 : 25,000,000. On gland cells histamine has a stimulating action eliciting on intravenous injection increased secretion of tears, of saliva, of bronchial mucus, and of gastric and pancreatic juice. If a drop of histamine solution in concentrations of from 1 : 1,000 to 1 : 100,000 is applied to the scarified skin, it produces within one minute, itching, reddening, and finally a large urticarial wheal which sends out pseudopodia-like processes and measures from 2.5-7 cm. in diameter. These wheals feel hard and resistant, are movable with the skin and cannot be removed by pressure. Subcutaneously, in doses from 0.5 to 1 mg., it produces erythema of the entire skin.

RELATION TO PHYSIOLOGY AND PATHOLOGY

The short description of the pharmacodynamic action of the two chief representatives of the proteinogenous amines will suffice to suggest the possible relationship these substances may have to human physiology and pathology. To accept this relation as a scientific fact developed on a sound basis without indulging in interesting but fruitless speculation, it is necessary to satisfy several preliminary inquiries.

1. Have these substances ever been found in the animal organism?
2. How are they formed?
3. What is their fate and function?

Before answering the first and most pertinent question, let us consider the second one. These amines were recognized as the result of putrefaction; this means they were formed from protein material by the action of micro-organisms. The bases were isolated from organs or tissues of animals, permitted to putrefy by being exposed in a haphazard way, either before or during experimentation to the ubiquitous micro-organisms, or organic material was for this purpose inoculated with a piece of putrid meat, most frequently with pancreas. Some of the workers in this field, recognizing the relation of the putrefactive amines to the amino acids, subjected a single amino acid to the action of bacteria and in this way gained a clearer insight into the chemistry of the process. The bacteria involved in this process remained obscure. In 1912, Berthelot and Bertrand isolated in pure culture from the human intestine a micro-organism which had all the characteristics of

the bacillus mucosus capsulatus (Friedländer's pneumobacillus), but in addition the faculty of decarboxylating histidine, tyrosine and tryptophane to histamine, tyramine and indolethylamine, and they therefore named this organism Bacillus aminophilus intestinalis. In the same year Mellanby and Thwort described a micro-organism belonging to the typhoid-colon group, capable of producing b imidazolethylamine from histidine. Theoretical considerations and preliminary experiments had convinced us five years ago that the ability to decarboxylate amino acids to amines could not be restricted to one or two species of bacteria, but that it might be found to be a fairly common property of micro-organisms provided that the chemical conditions of life were understood which called forth the formation of these basic products. Investigations on this problem, carried out in the Sprague Institute for Medical Research at the University of Chicago, in association with Dr. Hanke, have been published in part. We could show that the colon bacillus will form histamine from histidine only in the presence of an easily available source of carbon, such as glucose or glycerol; that the production of the amine is always coincident with the production of a medium that is distinctly acid, and we expressed the belief that the amine is formed by the micro-organism to neutralize the excess of acidity. It can therefore be accepted as a proved fact that micro-organisms, that have the faculty of forming poisonous amines from amino acids, live in the intestinal tract of man.

Can this decarboxylation of amino acids occur in the absence of micro-organisms?

The depressor action of certain organ extracts had been known for a long time. The work of Popielski had shown that such "vasodilatins" could be extracted practically from all tissues. In 1911, Barger and Dale reported that they had succeeded in isolating B imidazolethylamine from the extracts of intestinal mucosa; they showed that Popielski's "vasodilatin" contained histamine and also the depressor action of secretin of Bayliss and Starling could be explained by the presence of this base. The authors at first regarded histamine as a normal product of the intestinal mucosa, but later — under the influence of the work of Mellanby and Thwort — they adopted the view that the formation of the base is probably due to the action of bacilli.

This view is permissible, but it is extremely probable that the digestive cells of the mucosa themselves are able to decarboxylate histidine to histamine. It might be stated as a general principle that

any enzymatic activity possessed by bacteria is uniformly the property of some cells of the mammalian organism or that what the bacterial cell can do, the organ cell is able to do. If, therefore, micro-organisms possess a carboxylase activity, it is safe to assume that the multicellular organism too is possessed of this faculty of decarboxylation. In the disorder of proteinmetabolism known as cystinuria, the two diamines: putrescin and cadaverin, have been repeatedly found in urine and feces. There is no real evidence that in this condition the diamines are formed by the activity of bacteria from the two amino acids, lysin and ornithin (from arginin), and the view is generally held that the diamines, which cystinurics sometimes excrete, are the products of an abnormal protein metabolism. This conception receives very strong support through the studies of Loewy and Neuberg on a patient excreting cystin in the urine. At ordinary times no diamine could be detected in the urine, but when lysin was given to him by mouth, he excreted cadaverin in large quantities, and when arginin was given he excreted putrescin. Yet the absolute proof that the diamino acids were not decarboxylated by the intestinal bacteria, but by the cells of the organism could have been deduced only from the subcutaneous or intravenous administration of the amino acids. Unfortunately, this has not been done. Thus far it has not been definitely proved that sterile extracts or emulsions of organs like the liver harbor an enzyme of the carboxylase type, or that such enzymes are developed during the aseptic autolysis of organs.

The physiological activity of the hypophysis has been a subject of constant investigation since Oliver and Schaefer, in 1895, discovered that extracts of the gland had the power of raising blood pressure. And when it was shown, some years later, that such extracts of the pituitary body had the power of producing strong contractions of the uterus, a new agent was introduced into therapeutics. Ever since the isolation of the active principle of the gland has been attempted by biochemists, and their investigations have shown that the substance behaves like a base, the only precipitant to bring down the active principle being phosphotungstic acid. Fühner, in association with the other chemists of Meister Lucius und Bruening in Höchst am Main, claimed to have isolated four different crystalline substances, all of which showed physiologic activity in varying degree, and Fühner believes that there exist four active principles. His work, however, invites the

interpretation that these four active fractions owe their activity on the uterus to contamination, absorption or chemical combination with one and the same true active substance of exceedingly high potency.

The base precipitated from pituitary extracts gives the chemical reactions which characterize it as an imidazol derivative, and since B imidazolethylamine or histamine produces powerful contractions of the uterus, it has been considered quite possible that the active principle of the hypophysis is a polypeptid-like derivative of this base. In June, 1919, Abel and Kubota of Johns Hopkins, published a remarkable paper in the *Journal of Pharmacology and Experimental Therapeutics,* entitled: "On the Presence of Histamine (B iminazolethylamine) in the Hypophysis-Cerebri and other Tissues of the Body and Its Occurrence Among the Hydrolytic Decomposition Products of Proteins." In this communication the authors report the isolation of histamine from the hypophysis, and they consider it the plain muscle stimulating and depressor constituent of the posterior lobe of the hypophysis. They further claim to have demonstrated histamine in the gastric and intestinal mucosa, in the liver and skeletal striated muscle; having found it in Witte's peptone, they conclude that peptone shock is due to histamine and the authors are confident that the toxic principle of Vaughan's protein poison too is histamine. But this is not all of their claim. Convinced that histamine is one of the products of the enzymatic digestion of protein-containing foods, the authors make the extraordinary statement that they have obtained histamine on the acid hydrolysis of egg albumin, casein and edestin. To quote from their paper: "It is our opinion that this substance makes its appearance wherever living protoplasm exists, or at least wherever protoplasm is killed; in other words, that it arises wherever true protein is even partially disrupted by enzymes, acids or other hydrolytic agents." While such statements concerning the great importance of the amines coming from one of the foremost scientists of our country is extremely gratifying to us, who have worked on this subject now for nearly five years, we feel — on the basis of our work *— more than a little hesitancy in accepting Abel's results in their entirety. But this is not the time nor the place to debate differences of results due to differences in methods. We are in accord in our views regarding the fundamental significance of the proteinogenous amines for the physiology and pathology of the human organism. Regarding the fate of the protein-

* See our papers in the Journal of Biological Chemistry, 1920.

ogenous amines in the animal organism, we are still insufficiently informed. It could be shown by Ewins and Laidlaw that if p. oxyphenylethylamine is given by mouth to dogs, about 25 per cent. is eliminated in the urine as oxyphenylactic acid. It is known that the liver is the organ chiefly involved in this process of deamination and oxydation, for on perfusion of the surviving rabbits' liver, up to 70 per cent. of the theoretically possible acid was actually isolated. Similarly, indolethylamine is converted into indoleacetic acid on perfusion through the liver. The fate of B imidazolethylamine in the organism is still unknown. This katabolism of the amines to a fatty acid proceeds probably by way of the alcohol and the aldehyde according to the following scheme:

$$\underset{\mathrm{I}}{RCH_2NH_2} \longrightarrow \underset{\mathrm{II}}{RCH_2OH} \longrightarrow \underset{\mathrm{III}}{RCH{=}O} \longrightarrow \underset{\mathrm{IV}}{R-COOH}$$

By these transformations, these physiologically active substances are detoxicated, in the healthy organism, in the liver. Morbid conditions, then, will depend on the quantitative relationship of poisons produced and detoxicating function. The insufficiency of the detoxicating apparatus or an excessively large overproduction of amines might produce disease.

These are, in brief, some of the newer facts which the study of the proteinogenous amines has established. Their application to the more practical problems of clinical medicine, based on the use of the exact methods developed, promises a rich field. But I have deliberately abstained in my discussion from leaving the firm soil of the evidence gained by experiments to venture out on the perilous sea of supposition and speculation.

THE ORGANIZATION OF RESEARCH IN OUR AMERICAN DEMOCRACY

JAMES R. ANGELL
Chairman of the National Research Council

March 5, 1920

I

Hardly had President Wilson formulated our purpose in the Great War as that of making the world safe for democracy before voices were heard here and there urging that we should also make democracy safe for the world. The close of the war, with the crushing victory of the Allies, has seen increasing significance attached to this demand, and a new and more critical insistence on a satisfactory definition of "democracy" itself. It is, however, furthest from the intention of the present paper to attempt any philosophical exposition of the conception of democracy. For the purpose in hand, democracy is simply contrasted with autocracy as designating a human order in which the component individuals in theory, at least, determine the form of organization under which the community administers its affairs, as contradistinguished from an order in which some single individual or some small self-appointed group assumes these functions. It is the place of scientific research in such a form of human organization and a consideration of the practicable methods of safeguarding and promoting in the United States the interests concerned that constitute the subject of our present discussion.

Science in general, however defined in its abstract phases, is in its practical aspects simply the organized technic of human knowledge by which the community and the individual alike sustain themselves in the face of natural forces. Scientific research is the germinating vital principle by which this technic is constantly developed to meet more fully the shifting conditions of life, and to master more perfectly the forces of the environment. To eliminate it would be tantamount to the final stagnation of human progress and the production of a condition of substantial equilibrium, a withdrawal of the fruitful operations of intelligence, and a reduction of human behavior to purely stereotyped and habitual forms. Scientific research is, accordingly, in no sense an extrinsic luxury of the mind, nor does it merely reflect the play of intellectual curiosities; it is of the very life-blood of human

progress, the embodiment of the inner principle of intelligence itself. The maintenance of appropriate and fruitful conditions for its growth is therefore in the final analysis a matter of absolutely fundamental significance for humanity, and in a democratic order of society, it requires peculiar nurture because it appeals to the full appreciation of only the highly intelligent, and consequently stands in constant danger of being underestimated, with resulting loss of adequate financial and social support.

To discuss the organization of research in a democracy presupposes an affirmative answer to a preceding question and one to which, in the minds of many persons, a negative response should be made. There are not a few individuals, and among them many persons of high intelligence, to whom the intrinsic idea of research is foreign, and indeed hostile, to all thought of organization. They regard it as the field of purely personal initiative and as depending solely on individual fertility of imagination. They think of the occasional great inventor or discoverer as working in lonely isolation with the fruits of his own genius, and in the fullness of time passing these on to an eager humanity. To surround these elect of the gods with the trammels of organization of any kind whatever appears to them to be a sort of profanation, a sacrilege in the intellectual holy of holies.

A complete and convincing rebuttal of this position is perhaps impracticable within the limits of time at our disposal, but at least a few pertinent considerations may be submitted.

In the first place, it is unquestionably true that up to the present time, science has very largely relied for its advances on the individual worker and on relatively isolated effort in research. But, on the other hand, the evidence has been rapidly accumulating that in some directions we have approached the limits of profitable investigations on this basis, and while the final contribution must always be made by the resourceful intelligence of the individual worker, it is perfectly clear, both as a matter of theory and as a matter of accomplished fact, that in vast unexplored areas, the only effective procedure involves one or another of the forms of organization. Medicine offers some of the most striking demonstrations of this fact. It is a safe prediction that whereas the past generations of modern science have been chiefly characterized by individualistic effort in research, the next epoch will be quite as definitely characterized by cooperative organizations of various types. Prior to the war there had been certain instances of

organized research, especially under government auspices, which had achieved scientific results of unquestioned value. Certain of the geological surveys may be taken to illustrate this type of thing. But the war exercised a prodigious stimulation on the imagination of scientific men, and served to exhibit with conclusive thoroughness both here and abroad the indispensable nature of far-reaching cooperation and organization, in order to solve certain of the most urgent problems presented to a nation, whether in time of war or of peace. We have, therefore, definitely passed the point at which the merits of the organization of research need to be discussed as merely hypothetical. The limits of these advantages are still, to be sure, uncertain; the methods of accomplishing them are also far from definitely determined; but there can no longer be any question of the possible values inherent in such procedure.

We come at once then to the two fundamental issues in the whole affair. First, how shall there be established some agency for the stimulation and guidance of research, determining particularly how and where profitable cooperation may be brought about; and second, how shall research be financed? These two problems hang closely together, and in discussing the one, we shall in fact be largely concerned with the other. To make our considerations profitable in the time at our disposal, we must turn at once to the existing situation. Were we setting out with a brand new social and political organization, as is now being done in certain parts of the world, we might perhaps provide differently. But as a matter of fact, there are already many research agencies in operation, and our duty is rather to examine these to determine how far they comport with democratic institutions, and in what manner, if at all, they may be made to serve more fully their true functions.

In our own democracy we are far from having determined with finality what enterprises we shall administer through explicitly government agencies, and what we shall accredit to private initiative. Of late the pendulum has undoubtedly been swinging to the side of an increasing assumption of government control over interests hitherto privately administered, but it does not at all follow that this process will ultimately eliminate all privately controlled enterprises; in other words, it does not follow that the general principles of democracy need eventuate in the extremer forms of socialism. There can be no practical doubt that for the next generation at least, the supervision

of scientific research will in large degree be left to nongovernmental agencies. Moreover, it is to be remembered that many results intrinsically based on democratic principles of procedure may be attained without employing the political instruments of democracy. The practice of medicine, for example, is generally conducted under certain regulations established by the government, but its actual conduct is, for the most part, in the hands of individuals or organizations quite separate from any political connection. The community patronizes these individuals and organizations or not, as it chooses. In this, its action comports with that freedom of personal choice so integral to all conceptions of a democracy. But the form of the action has no political significance. We may therefore assume that any process which is free from autocratic coercion, and in which the welfare of the community is given dominant consideration, complies with the democratic spirit and ideals.

II

Without pretense of literal completeness, it is safe to say that the principal research agencies in the United States are the following: (1) Federal scientific bureaus with their accessories; (2) state bureaus, experiment stations, and scientific commissions; (3) universities and professional schools; (4) privately endowed research institutes, including certain museums; (5) industrial laboratories and research organizations. This list omits the small but occasionally significant group of independent scientific workers, whose number is in this country so inconsiderable as properly to be disregarded in connection with this analysis. It also omits state and municipal academies, a few of which have some significance for research.

1. In the nature of the case, the federal scientific organizations necessarily proceed under government direction. This does not preclude their entering from time to time on cooperative relations with other organizations, but it does in general limit such cooperation to purely informal and incidental forms. The scientific achievement of any one of these bureaus is largely dependent on the character of the director, who is necessarily an appointee of the political party in power at the time of his selection. Despite certain notorious exceptions, the general caliber of these bureau chiefs has been excellent.

The history of the development of these bureaus has been one of slow growth step by step, now some energetic individual with imagination and magnetic persuasiveness inducing Congress to furnish the

necessary funds; again, some great group of vested interests insisting that the government come forward and furnish needed scientific assistance. Once established, Congress has generally been ready to continue appropriations to these bureaus, but the increase of such appropriations, which must inevitably follow a healthy growth of the work, has not been so easy to secure.

Now as a matter of democratic theory, much is to be said for alloting to the federal government the great burden of responsibility for scientific research in those fields obviously affecting the public interest. But practically, we have not yet reached a stage even approximating such conditions, and certain present limitations under which these agencies operate must be recognized.

In the first place, then, it is difficult to persuade Congress to make appropriations for branches of science which do not rather conspicuously affect the great mass of people. The niggardly appropriations which have generally been made available to our State Department reflect this spirit. It is not obvious just how the inhabitants of Fox Corners or Bear Gulch are benefited by competent representation in foreign capitals, and until it is, the average congressman is not going to be greatly interested in the matter. The same principle operates in the appropriations for science, and especially for research. It is fair to say that the more recent sessions of Congress have shown appreciable development in this matter, but the conditions are still far from satisfactory.

In the second place, and quite as important, is the fact that the scientific bureaus inevitably find themselves put under severe pressure to deal only with problems of immediate practical importance. The time of the staff of many of them is monopolized by replying to inquiries. This is all quite as it should be, if there were at the same time provision for other kinds of work. Nothing is more certain than that research work devoted purely to practical problems is sure in the long run to go stale, and to exhaust itself in petty trivialities. The great revolutionary discoveries and ideas come from the cultivation of investigations in pure science, and generally without regard to possible practical utility. No one can for a moment question the indispensable value of research in applied science, nor that investigations in this field constitute a legitimate expenditure of government funds; but the other consideration is equally true, and in the long run even more significant, to wit, that a nation which disregards the interests of

research in pure science will find itself outstripped by its competitors in the modern world. To the well-informed, there can be no question, therefore, that in the selfish interests of democracy itself, research in pure science should be a matter of the utmost solicitude; but it is equally clear that under contemporary American conditions, the amount of this work that can be done under immediate government supervision is relatively small. For this part of our general national program of research, we must, for the time being therefore, look elsewhere.

2. What has been said in the preceding paragraphs regarding the scientific enterprises of the federal government holds measurably true of the corresponding work carried on by the states. As would naturally be expected, there is a wide diversity of practice among the different states, both as regards the number and scope of these scientific undertakings, and as regards the quality of the men to whom they are entrusted. Geological surveys, public health commissions, sanitation boards, highway construction commissions, drainage commissions, and agricultural experiment stations — these will suggest some of the multifarious directions in which the state has interested itself in scientific work. Properly enough, these undertakings, like those of the federal government, have generally been conceived in the interests of immediate practical results; but as a matter of fact, a good deal of their work has necessarily been of a research character, and at times small fragments of it have been such as might reasonably be included in the ranges of pure science. In states which support universities, there is oftentimes a very intimate interrelation between these state scientific bureaus or commissions and the scientific authorities of the university. Indeed, in some cases, the university operates in a particular field as the sole scientific agent of the state. Moreover, Congress has in recent years been appropriating increasing amounts of money for the furtherance of engineering and agricultural projects, most of which are by legislation conjointly administered by the states and the federal government. There is consequently a good deal of overlapping in these state and federal interests, which for the purposes of the moment we must largely disregard.

So far as these state scientific organizations undertake research work, the limitations mentioned in connection with the federal bureaus are even more in evidence, and certain others are superadded thereto. Not only is the pressure for immediate practical results probably greater, and the tendency to take the short-sighted rather than the far-

sighted view thereby increased, but there is also, owing to the more unstable political situation, less stability of official tenure and consequently less satisfactory conditions of work. Even where the mere tenure is adequately protected by civil service regulations, the ability of the political authorities to interfere by withholding appropriations, or otherwise embarrassing the scientist, is of more serious consequence. Generally speaking, the salaries paid have been also relatively less satisfactory, and the sum total of all these influences has been the reluctance of the abler men to go into such offices.

On the other hand, there is to be set over against all this the unequivocal fact that much admirable work has emanated from these scientific agencies, that a good deal of it has been of a research character and of excellent quality, and that granted a thoroughly intelligent public opinion, there is no reason why the scientific interests of the several states should not be developed to a high degree of perfection. If the state can be taught to conceive of its university as in some sense the capstone of its scientific work, and can be induced to recognize the indispensable part played by research in pure science, as well as the value of applied science, the benefit to the community can hardly be exaggerated.

Meantime, it is quite clear that because of the often arbitrary character of the state boundary lines, there is great need for the most intimate cooperation as between the scientific agencies in adjacent states. Moreover, it is probably practicable, by a reasonable adjustment of scientific plans, substantially to reduce the expenditures undertaken by adjacent states for identical forms of scientific work. The line which separates northern Illinois from southern Wisconsin is not one which has any relation to geology, agriculture, or animal husbandry — all of them economic and scientific interests of fundamental significance for both states. Abundant other illustrations will readily suggest themselves of the same sort of thing. Clearly, it is the duty of all good citizens to promote as far as possible an intelligent public appreciation of these matters, to the end that we may rapidly pass from the present somewhat disorganized and incidental attack on our national scientific problems to the level of a well-organized, inclusive, and intelligently directed program.

3. Our universities and professional schools present a bewildering complexity of conditions, both as regards their historical development, and as regards their internal organization with reference to scientific

work. Many of the strongest of these institutions are established on private foundations, frequently under sectarian direction, while others, and this a group growing rapidly in numbers and power, are entirely dependent on the state for support. As distinguished from all other research agencies, the universities, in addition to conducting a large part of the present investigations in pure science, are also the sole souices from which trained personnel is at present derived. This double function is often overlooked, but it is of peculiar significance for our democratic institutions.

Despite the fact above alluded to, that many of these institutions derive their support from private munificence, practically all are conducted in accordance with the spirit of democratic institutions in that they are seeking, so far as they are able, to serve the real needs of the community. For our purposes, we may therefore disregard this distinction based on the sources of their income. Certainly the problem that presents itself in the state-controlled and the privately controlled institutions is, so far as concerns research, of a substantially identical character. The differences that mark off one group from another in this regard are no greater than those that separate some of the members of each group from others in the same group.

As one goes about the country visiting these institutions, it becomes apparent that they differ widely among themselves in the degree to which there is in their atmosphere any appreciation of the real importance of research and a fixed resolution to cultivate it. In an unfortunately large number, the sheer routine of instruction is so urgent, and the obligation to care for the vast numbers of students who are enrolled is so pressing, that neither resources nor leisure can be commanded to care for the needs of research. In others, the conditions are far better, but there is none in which the situation is altogether ideal.

Two great groups of needs, the one substantially personal, the other institutional, confront the scientists in these institutions, and if they be not supplied, the future of science in this country must inevitably suffer gravely. The issues are so closely related that in practice they are hardly to be severed, but they deserve a brief separate discussion.

In the first place, there is at present, with the most infrequent exceptions, no adequate provision for the research man to secure sufficient uninterrupted time for his work. This limitation is generally

combined with insufficient resources for apparatus and assistance, and with seriously inadequate salary, a difficulty from which all academic men are now suffering, but it is peculiarly disastrous in its effects at this point, because the ablest research men are certainly rarer than the men who can carry respectably the work of instruction, and the loss of a few such men from the field of science entails relatively greater permanent loss for human progress. This is but another way of saying that in general our universities have never genuinely accepted the obligation to carry on research as at all equal to the obligation to give instruction.

In the second place, there is at the moment an altogether unintelligent type of competition among universities for the development of varied forms of research. It is of course to be recognized that certain great fundamental intellectual interests must be represented in the instructional work, at least, of every institution calling itself a university or even a college. But it does not follow that each such institution should undertake to develop research in all possible lines. From no point of view can the present wastefulness in this matter be justified, and unless it be corrected by voluntary cooperative effort, it is bound to lead to enduring disadvantages, not to say disaster. Let us take, without intent to be invidious, such a field as vertebrate paleontology. The scientific importance of this branch of work no one can possibly call in question, but on the other hand, it is perfectly clear that to attempt to supply every university with the resources and the personnel for thoroughly satisfactory research work in this field would be to the last degree wasteful and absurd. Many other illustrations of a similar character will suggest themselves. The universities can hardly justify themselves, nor can the scientific men who compose their faculties do so, in the persistent demand for unlimited increase of financial resources for research until they have elaborated a reasonable program for the ditribution of responsibility for research work.

Mention was made at an earlier point of the obligation of the universities to train competent research personnel. This obligation involves not only the preparation of such personnel in requisite numbers to meet the demands of the modern community, it also implies an obligation to exercise an adequate selective process by means of which those who are properly endowed in point of intellectual power shall be attracted into research work as a profession, while the unpromising and unfit shall be eliminated.

So long as the financial and social rewards of a research career do not compare favorably with the other obvious opportunities open to men of intelligence, no devices which can be applied at the training level will solve the problem. But assuming that society has come to recognize the indispensable character of this service and to reward it appropriately, there still remains the necessity of developing adequate selective methods during the period of university training.

The common device thus far employed to attract competent men into research has been the fellowship or the paid assistantship. Both of these are sufficiently familiar to require no discussion, and it probably requires no detailed demonstration to justify the statement that neither device has proved at all adequate. Stipends for fellowships have generally been too small either to attract the ablest men or to enable them to give their undivided time to research or the preparation for research. Assistantships are, at a certain point in a research man's training, of peculiar value, but they rapidly lose their importance as training proceeds and, save in a few instances, have been too poorly paid to encourage, or in some instances even to permit, competent men to take them. Furthermore, as generally administered, both forms of aid to research workers have been given at a very early stage of their development and often before they have in any wise justified complete confidence in their final fruitfulness. There is therefore unquestioned need of some form of financial support and professional recognition for men who have already received the Doctor of Philosophy degree or its equivalent, and who are ready to carry forward into actual execution investigations to which their previous work has led them. Hitherto the common fate of men at this stage of their training has been to be diverted into impossible burdens of teaching, or equally distracting purely professional work.

An experiment is now being made by the National Research Council in the fields of physics and chemistry whose results will be watched with the greatest interest. This experiment involves the selecting of a small group of men of the general grade described above, who have given high promise of achievement in research, and subsidizing them for a period of four or five years with adequate living salaries, during which time they may give themselves wholly to scientific investigation. Out of this group it is believed there will emerge many of the most valuable contributors to the development of research in the sciences

concerned, most of whom would otherwise have been lost to the drudgery of teaching, or to the allurements of professional life, or to the industries.

Whatever methods are in point of fact selected may well be left to the determination of those immediately in charge of our training institutions. But it is extremely important that they should feel the pressure of public opinion compelling them to face this process of stimulation and selection as an absolutely essential part of their work. One meets too frequently the attitude of complete laisser-faire, the disposition to let nature take her course and to feel little concern as to what that course may be.

4. Of late years private benefactions have not infrequently been attracted to the establishment of research institutes. These have represented a wide variety of scientific fields, for example, chemistry, geophysics, terrestrial magnetism, astronomy, botany, zoology and particularly medicine. Certain of the great museums also carry on a laudable amount of research in various branches of natural science. No one can question the extremely valuable results that have come from the work of these institutes, and in the minds of many people they have seemed to furnish the most rational solution of the problem of organized research. As contrasted with the educational institutions, workers in them are entirely free from the distractions of teaching. They are, moreover, as a rule, fairly well paid, comparing, on the whole, more than favorably in this respect with academic men. These organizations are generally administered with a fine sense of public obligation, and, unlike the state and federal bureaus and stations, many of them are quite free from pressure to pursuue investigations in applied as opposed to pure science. As an expression of the wise spontaneous expenditure of wealth, they constitute a peculiarly encouraging example of what may be expected in a democracy that leaves much to private initiative. But the disadvantages of these institutions, while less obvious than those of the other agencies already mentioned, are not less real.

In the first place, the cost of administering scientific research on any large scale is too staggering to be cared for by institutions of this type when the entire field of science is taken into account. Moreover, there are some unequivocal disadvantages for the worker in certain of them in his isolation from a wide range of scientific companionship and in his freedom from the necessity of constantly maturing for

presentation to a competent body of colleagues or students the results of his investigations. Most serious of all, perhaps, is the fact that these institutes are consumers merely of personnel. They train their own men in their own particular technic, but they do not give fundamental training; for this they are obliged to rely on the universities. In this regard they are inevitably sterile, and while this does not lessen their value from the point of view of mere scientific productivity, it does materially affect their general position among the mechanisms for the production of scientific research. They must, therefore, be regarded as highly valuable elements in the contemporary situation, but as affording in no sense a complete solution of the problem of research in a democracy.

5. There remains to be mentioned the case of the industries for which research work is of critical consequence. No small part of the conspicuous position that Germany had gained for herself prior to the war was due to the extent to which, largely through government subvention, she had fostered industrial research and had brought into intimate organic contact inventors in pure and in applied science. Taking a lesson from her book, Great Britain, Italy, Japan and Canada — to mention no others — have entered on well-considered programs of industrial research with government subsidies to back them. It is certainly high time that the United States took cognizance of this situation and prepared to meet its consequences which will inevitably be shortly apparent in a severer rivalry in the markets of the world.

Under contemporary conditions in this country one must sharply distinguish from one another two sets of quite diverse circumstances. There is on the one hand the great industrial corporation with its own research laboratories and its own staff, in some cases including hundreds of men. There is in the second place a great group of industrial enterprises that either have no scientific laboratories, or have such conducted on so meager and purely routine a level as to be of negligible consequence. There is a large amount of missionary work to be done in the first group, for, astonishing as it may seem, some of the extremely important and fundamental industries organized on a large scale have been strangely negligent of the possibilities of scientific assistance. It is in the second group, however, that the largest opportunities exist, and here one or another of the cooperative devices must probably be employed. There are at the moment several conspicuous instances of this type of thing, in which a group of com-

panies, no one of which could possibly afford to finance the operation alone, have combined to conduct a joint laboratory or to employ jointly a staff of scientists to carry on for them essential research in the industrial processes which they use. There is almost no limit to which this device can be developed and there is no question whatever but that the industries will benefit immensely by the results of such undertakings. Ultimately, the community itself is sure to benefit. The converse of this picture, assuming that the industries fail to make proper use of scientific research, is not only the stagnation of industrial enterprise itself, but also the loss of that place in the markets of the world which we have hitherto won.

There is no question in anyone's mind that under the present economic organization of society it is far better that the industries should meet the cost of research such as we have been considering. Certain research work undertaken through government auspices is capable of exploitation by the industries, and the same thing is true of not a little of the research conducted in universities. To this appropriation of knowledge and skill no one is likely to raise serious objection, but on the other hand there is equally no question that the industries should and will bear the great burden of this expense for research in applied science.

A much more interesting question concerns the extent to which the industries may be asked or expected to contribute to research in pure science. Superficially considered, the attitude of the head of a stock company who urges on his board of directors investment in scientific research can only be justified if he can with substantial conclusiveness demonstrate that such an investment will pay dividends, and do so in sufficient measure to justify the expense. While this is undoubtedly a correct estimate of the situation as it appears at first inspection, a little further consideration of the matter will lead to a broader and somewhat revised verdict. In the first place, it is perfectly clear that the personnel required in the scientific work of the industries can only be recruited from the universities and technical schools. There is therefore resting on the industries a purely selfish obligation, leaving alone any more generous conception of their obligation to the community as a whole, to aid in the support of the institutions from which they secure their scientific staff. But more important still is the consideration that while no one can predict the practical value of any particular discovery in pure science, it can be conclusively shown that only

through investigations in pure science is large and constant progress in the technic of industrial processes to be secured. While it might therefore be difficult to make a good case for the demand on any isolated industry taken alone to give support to researches in pure science, a strong case can be made for the duty, as well as for the demands of merely selffish interest, of the industries as a whole to support such research. This conclusion follows almost inevitably if one conceives of the industries as subserving an essential function in the life of a democratic community, intead of conceiving them, as is so often done, as representing merely the improvement of opportunities to exploit this community. Wise and liberal-minded leaders of the great industries are already coming to take this wider and more far-seeing view.

III

The institutions and organizations that have now been discussed are those in which the actual work of research is for the most part conducted in this country. There is, however, another group of agencies, whose personnel is substantially identical with that of the groups previously mentioned, which nevertheless occupies a distinctly unique position in its relation to the promotion of research. I refer to the scientific societies, some of which are explicitly dedicated to the furtherance of research interests and practically all of which have at one time or another concerned themselves with these interests. Their activities cover a wide range, at one extreme perhaps being characterized by occasional meetings of a dominantly social character, and at the other extreme by the subsidizing and administration of definite pieces of research. We have had for many years in this country a federation of these scientific societies, the American Association for the Advancement of Science, which has by no means been inclusive of all, but which has possessed representatives from a very broad field. Similar organizations exist in other countries, and reflect the general modern recognition of a continuity of interests in all scientific work.

The personnel of societies such as these being, in theory at least, chosen for merit in the form of scientific accomplishment, evidently sustains a relation of peculiar potential value to the scientific development of our democracy. It is clear that only from this group, formed by natural processes of segregation, can be expected any considerable and uninterrupted contribution to the methods of human progress. An interesting experiment is being conducted in this country in the

effort to capitalize the energies and resources of these societies to supply certain features that are obviously lacking in our national facilities for research. I will speak of it briefly.

In the preceding chapters, I have pointed out the more obvious characteristics of our present agencies for the conduct of scientific investigation, attempting to indicate briefly their strength and their weakness. Assuming that this sketch has been essentially accurate, it will be recognized that while admirable provision is now made for research in certain of its aspects, there has been no general organization of these interests and no agency in any way responsible for their systematic development. To achieve just these ends, the National Research Council, organized during the war as a war measure, and operating under the charter of the National Academy of Sciences, has been established in perpetuity with an endowment of $5,000,000 given by the Carnegie Corporation of New York. It has also received nearly a million dollars in the last few months from other agencies, to wit, the Rockefeller Foundation, the General Education Board, the Commonwealth Fund, and a number of private individuals. The Council is built on the foundation of the national scientific societies, upward of forty being represented in its constituency. It is their instrument, so far as they choose to use it, for the promotion of research, and especially, where this is practicable and desirable, for the promotion of cooperation among research agencies. It is composed of seven Divisions of Science and Technology, including physics, mathematics, astronomy, engineering in all its branches, chemistry and chemical technology, geology and geography, medicine, biology and agriculture, anthropology and psychology. Each division is made up of scientists elected by the appropriate societies and a certain number of members at large. These men choose a chairman, who becomes a salaried officer of the Council, resident for a year or more in Washington. In conjunction with his executive committee, it is the duty of the chairman to carry out the policies adopted by his division. Working side by side with the representatives of other sciences, it is relatively easy for these chairmen to get together for cooperative work, as well as to secure criticism and suggestions on research enterprises affecting any field whatever of natural science. Most of the great scientific problems affecting the modern state or community traverse several quite distinct sciences. Public health problems afford abundant instances of this fact, running out as they do from medicine

into engineering, chemistry, bacteriology, entomology, and the like. Food, nutrition, water supply, drainage, and fuel offer countless other instances of these same overlappings of scientific problems. Under the National Research Council organization, all research work is purely voluntary. There is no coercion, no attempt to monopolize, or dictate, or in any other objectionable manner to control the individual, or the direction of his research. But on the other hand, there is brought to bear the most competent professional advice concerning the problems whose solution is most urgent, and detailed plans are formulated for the attack on such problems. Invitations are then issued to men and organizations to cooperate in the solution of such problems. If they accept, they then become part of a general scientific program, and the results which they gain are incorporated in this total project. The only kind of initiative which they lose is that which anyone abandons the moment he commits himself to one piece of work rather than another.

The Council has also a series of six so-called General Divisions, which cut across the Divisions of Science and Technology, and represent the contacts of each of these scientific divisions with some of the larger phases of the government, the state, and the life of the community. These divisions are respectively entitled Government Division, Division of Foreign Relations, Division of State Relations, Division of Educational Relations, Division of Research Extension, and Research Information Service. This is neither the time nor the place to elaborate on the functions of each of these general divisions, but a single word may be said in explanation of each.

The Government Division is made up of representatives of each of the scientific branches of the federal government, including all the technical divisions of the army and navy. It is intended to afford a medium for the informal contact of the personnel of these branches of the government service with one another, for the furnishing of a channel through which, if they choose, they may enter on cooperative scientific undertakings, and finally, a means whereby they may be brought into direct contact with the great group of nongovernmental scientific agencies.

The Division of Foreign Relations is responsible for the maintenance of satisfactory international scientific affiliations. There was held at Brussels in July, 1919, the first meeting of the International Research Council, in the formation of which our own Council had

taken a commanding part. The International Research Council will take the place of the old international unions, which were practically destroyed by the effects of the war, and the Foreign Relations Division will operate as the central clearing house for the administration of these international affairs. It will presumably be used by the State Department as its agent in many matters of international consequence.

The States Relations Division is intended to further in every possible way the interests of the organization of science inside the states, and wherever this can be done to advantage, the promotion of cooperative interests among the several states.

The Division of Educational Relations is especially devoted to the advancement of the conditions of research in the institutions of learning, with particular regard to the development of a satisfactory research personnel, and the promotion of the best conditions for research in pure science in such institutions.

The Division of Research Extension is particularly concerned with the promotion of scientific research among the industries.

The Research Information Service represents an attempt to better all of the devices by which scientific knowledge is made available for those who need to use it, not only such knowledge as is already to be found in texts and in printed documents, but also much that is not there to be found, such as the status of current researches, the location and competency of research personnel, and dozens of other facts of that kind not available anywhere in this country. The plans of this division also involve fundamental improvements in indexing, abstracting, and in the general manipulation of bibliographical materials.

It will be seen at once that any Division of Science and Technology, such as engineering, for instance, touches the work of each one of these General Divisions, so that the title of the latter does not so much indicate any lack of concreteness in the work they are doing, as it does the fact that this work touches a great range of interests.

In a democracy like our own, we enjoy the unquestioned advantages that spring from wide opportunity and the high premium put on individual initiative. In all undertakings in which these two circumstances are crucial, we outstrip all competitors. But our success is purchased at a price, and that is one which materially affects such interests as those of scientific research calling, as these do, not only for the highest forms of trained intelligence, but also for coordinated effort, on a large scale, of individuals and organizations for the most part devoid of direct relations with one another. Even a superficial

survey of the situation discloses that we need the most drastic stimulation to secure an increased social evaluation of the place of research in our national life, a greatly augmented productivity of the present research agencies, and a much more effective coordination of those agencies, both with regard to planning and with regard to executing the broad inclusive investigations required by our modern life.

The National Research Council is making a modest beginning in the effort to render the services indicated by these requirements. How well it is to succeed remains to be seen; but representing, as it does, practically all the scientific men of the country, there is no reason why, if its present organization and methods are unsatisfactory, these should not be modified and improved. In the meantime, it enjoys the prestige of a truly national basis without the limitations which are inseparable from a strictly government organization.

As a result of our analysis, we may summarize our estimate of the present situation as follows:

While the government agencies, both state and federal, supply an appreciable amount of the scientific service now required by the nation, they are materially defective on the side of research, and especially in the direction of investigations in pure science. The other agencies are moderately successful, each in its own field, but none are at all filling the needs of the community. Expansion is sadly needed in almost every direction, and especially coordination of effort. This is as true of applied and industrial scientific research as it is of the investigations in pure science. Our universities in particular need instant and radical assistance, and a wise distribution of responsibility among themselves for different kinds of research work, otherwise both the quantity and quality of research personnel will decline to a fatally low state with a consequent wreckage of research itself. This is a matter demanding the immediate attention of all patriotic citizens. In research, perhaps more than in any other interest of national consequence, it is important to stress the spirit of democracy rather than its political forms. The more it can be conducted under voluntary and unselfish auspices, the better the result, the freer and the more spontaneous its contribution. But unless it be directed with due regard to continuity and organization of effort, there will be inevitable waste and delay in the achievement of large and enduring results.

TABLE OF CONTENTS

The Proceedings of the Institute of Medicine of Chicago are published at irregular intervals. For the present copies are distributed without charge to a limited number of libraries.

Address all communications in regard to the Proceedings to 637 South Wood Street, Chicago.